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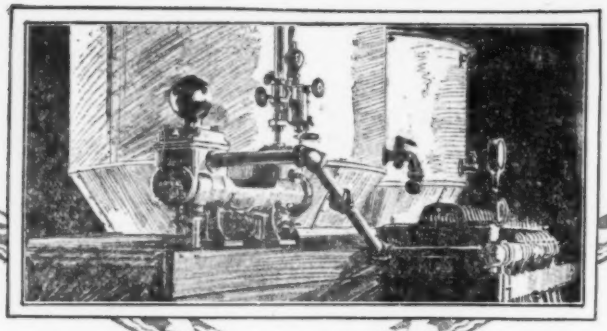

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STUDIES IN NEUROLOGY

I. The Phylogenetic Continuity of the Central Nervous System[1]

SVEN INGVAR

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Most of us have learned to recognize the cerebellum under the names applied to it by the old classical anatomists. We recall those very significant terms, vermis, pyramis, tonsilla, nidus avis, the digastric lobe, and others, that had such a strong appeal to their fancy. These names were for centuries undoubtedly only veils to cover ignorance; instead of assisting, they hampered the gaining of an insight into the organ, its nature and function.

Our knowledge of the cerebellum was considerably increased in the nineties by embryological investigations, more especially by English workers—Stroud, Bradley, Elliot Smith; but with Bolk's studies of the comparative anatomy of the organ a new era begins. Bolk's merit will always be that he revealed the morphological system of the mammalian cerebellum. He taught that the cerebellum was formed in all mammals on the same uniform principles. He divided the organ into two main divisions, the anterior and the posterior lobe. The margin between these lobes is formed by the primary sulcus, which well deserves its name by being in all mammals the first fissure to appear in the cerebellar primordium and the deepest of all transverse cerebellar fissures.

The anterior lobe is characterized by its rather simple external structure. Its lamellae are plain and extend with the fissures transversely through the organ from side to side. Bolk found that this anterior lobe was subdivided in all mammals into four smaller lobes corresponding to the lingula, the lobulus centralis and the culmen of the old nomenclature. Even from its external aspect one gets the

[1] First Herter lecture delivered at the Medical School of the Johns Hopkins University, November 3, 1927.

impression that the anterior lobe forms a very important part of the organ.

The rostral part of the posterior lobe, just behind the primary fissure, is built on the same plain pattern as the anterior lobe. Bolk therefore calls it the lobulus simplex. Behind the lobulus simplex the genuinely intricate structure of the organ begins. The main feature here is that the median part, the lobus medianus posterior, is separated by sagittal fissures from the lateral parts, the lobuli laterales posteriores. The former corresponds to the vermis inferior with its nodulus, uvula, pyramis, declive, and culmen of the human anatomy. The lateral lobes are very important, since they correspond to the hemispheres of the old terminology. They are formed on each side of the organ by ribbon-like convolutions of lamellae, the so-called ansiform lobe. This has two parts or crura, the anterior and the posterior, which fuse with each other laterally. The posterior crus passes over into a ribbon which lies parallel to the vermis in its posterior region—the lobus paramedianus. Connected with this there is at the posterolateral margin of the organ another very characteristic prominent gyral formation, pars floccularis or the floccular region, composed of the paraflocculus and flocculus. In the majority of mammals these form the most lateral parts of the cerebellum. Bolk called them pars tonsillaris and pars floccularis, respectively, because he supposed them to be homologous with the tonsil and the flocculus of the human brain. These are the main lines of the morphological system of the mammalian cerebellum as given by Bolk.

In 1917 I began in the Brain Institute of Amsterdam (Director, Dr. C. U. Ariens Kappers) a comparative study of the cerebellum of the vertebrate phylum, including the amphibians, reptiles, birds, and mammals. In this lecture I can deal only with the most important parts of my investigation, but must refer those interested to my work published in the *Folia Neurobiologica* (1918). (Zur Phylo- und Ontogenese des Kleinhirns nebst einem Beitrage zur einheitlicher Erklärung der zerebellären Funktion und Lokalisation.)

Among the subjects that were taken up in my comparative studies was the cerebellar ontogeny of the fowl. This had been investigated by some of my predecessors, who had maintained that the sequence of

the cerebellar fissures in this animal was so rapid, that it was not possible to check up the different stages in the development of the different cerebellar lobes, so easily followed in the case of the mammals. By selecting several specimens from about the same embryonic age I obtained a complete series that showed the development of the organ from a simple disc until it had reached its final lamellation. This study showed that the cerebellum of the chick develops on exactly the same principles as the mammalian cerebellum. In this way I came to the natural conclusion that the avian organ must be, at least in its most important parts, homologous with the mammalian. The resemblances in the architecture of the organs are too many and too detailed to be caused merely by hazard. There must be a complete anatomical correspondence of the cerebella in the two classes.

I was impressed by the fact that in their development the anterior and posterior regions of the organ followed almost identical lines. They developed their transverse fissures contemporaneously, whereas the middle region received its fissures and its configuration later. This was so striking that I ventured to suggest a subdivision of the organ into three lobes, the anterior lobe, the posterior lobe and, between them, the middle lobe. I hope in the following pages to be able to justify still further my subdivision of the organ into three lobes, instead of the two main lobes of Bolk, as being more in conformity with its real structure and functional organization.

The anterior lobe of the avian cerebellum proved to be constructed in four smaller lobes exactly as in the mammalian. And in the posterior lobe there are the same three main parts as in the mammalian. It is characteristic of the mammalian posterior lobe that it fuses laterally with the floccular formations by means of the velum medullare posterius. The flocculus is built directly on the rostral edge of the lateral process of the fourth ventricle. In the same way the posterior lobe in the chick passes over laterally into formations, the auriculae, which have the same relations to the lateral process. The external resemblances between the anterior and the posterior lobes in the mammalian and the avian cerebellum are in fact out-standing. By examining about fifty different species of birds I was able to show that the anterior and the posterior lobes showed a striking conservatism. They were built all in the same way, whereas the middle

lobes varied considerably. Briefly, it could be stated that any new higher development of this organ in the birds manifests itself almost exclusively in the middle lobe by a richer lamellization. This lobe is not only ontogenetically but also phylogenetically the youngest part of the organ. I wish to lay stress upon this fact thus early, because

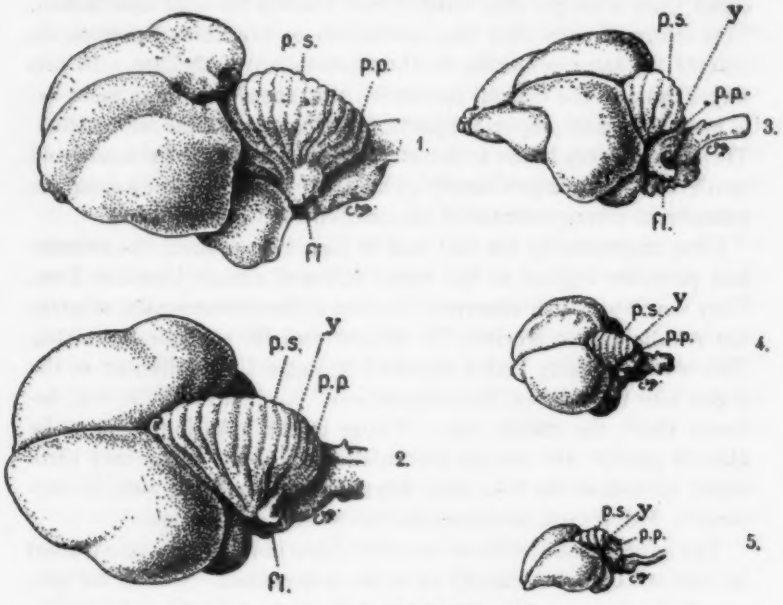


FIG. 1. CEREBELLA OF VARIOUS BIRDS

1, Dromaeus Novaehollandiae; *2*, Sula bassana; *3*, Eulabia indica; *4*, Nucifraga; *5*, Ottocampsa leucotis. *pp.*, lobus posterior. The fissure *y*, which separates the posterior lobe from the middle lobe, is the more conspicuous, the smaller the birds.

in my opinion it reveals a very important general principle for the central nervous system. *Whenever a homogeneous area within the central nervous system undergoes a higher differentiation, this appears not in the marginal regions but in the centre as an excentrical development.* Of course I do not deny a higher development also of the marginal regions, but I would emphasize the fact that the most important

differentiation is, so to speak, focussed in the central regions. This principle has its bearing not only on the cerebellar but also, for instance, on the cerebral cortex where it helps us considerably in getting a survey of the general arrangement and the organization of this extremely intricate formation, which will shortly be dealt with more fully.

It was evident that the homology so clearly demonstrable in the cerebella of birds and mammals should be of great theoretical value for the cerebellar problem as a whole. Birds and mammals are, as we know, to be considered as branches of the phylum which have diverged very early in evolution. We are, therefore, entitled to conclude that the common ancestor, wherever it is to be sought in evolution, must *in nuce* have had a cerebellum, in which the fundamental principles appearing in the higher animals are laid down. Thus, we may, for instance, be justified in looking for the same morphological features in the cerebellum of the reptiles. As a matter of fact they are to be found there. The cerebellum of the alligator has only two transverse fissures dividing it into three parts and there are reasons for homologizing these with the three lobes of the birds and mammals. The alligator is the first animal in the vertebrate series that shows transverse fissures. But even in the still more primitive reptiles, without any transverse fissures, *e.g.* the lizards, the same morphological principle holds, as was pointed out by me in 1918 and later corroborated by Olof Larsell.

From my findings of the evolution of the avian cerebellum I began a more detailed study of the mammalian cerebellum. This was thoroughly investigated by Bolk, as mentioned above, but he had occupied himself only with the mammals. The new views that presented themselves in my studies of the avian cerebellum also proved to be fertile when applied to the mammalian organ. It was clear that the mammalian cerebellum must necessarily also be subdivided into three main lobes. The anterior lobe is separated from the posterior part of the organ by the primary fissure, as indicated by Bolk. But this posterior part—the posterior lobe of Bolk—can naturally be divided into two lobes. Looking at the most caudal parts of the vermis, the lobules that in human anatomy are named nodulus, uvula, and pyramis, we find they have the same external design, whereas

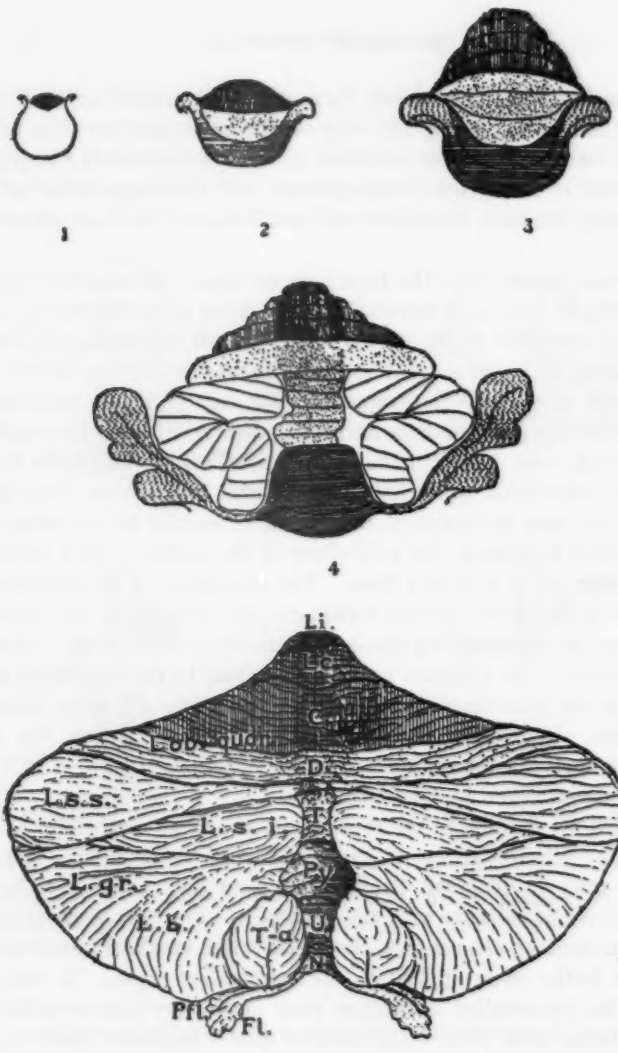


FIG. 2. DIAGRAMS OF THE CEREBELLUM OF (*1*) LACERTA; (*2*) ALLIGATOR; (*3*) BIRD; (*4*) MAMMAL; (*5*) MAN; SHOWING THE HOMOLOGIES IN THE CEREBELLA OF ALL THESE VERTEBRATE CLASSES

Vertical lines: lobus anterior. Horizontal lines and stipplings: lobus posterior. White area: lobus medius.

the parts lying rostrally to them—the declive and culmen—have in many species a quite different pattern. The nodulus, uvula and pyramis have much coarser lamellae than the declive and culmen. I suggested calling the former the posterior lobe and the latter the median lobe as in the avian cerebellum. The former are separated from the latter by a very definite fissure, which, on account of its topography, has received the name of the prepyramidal fissure. The posterior parts of the vermis could be shown to have the same relation to the floccular region as the corresponding parts in the avian cerebellum. They fuse laterally with the floccular region by way of the velum medullare posticum. I came to the conclusion that this velum must be considered as belonging to the old cerebellum, having in the highest vertebrates been submerged by strongly developing parts, the paramedian lobe, or the tonsil, lying rostrally to it.

The most salient feature of the mammalian cerebellum compared with that of the lower animals is the appearance of the hemispheres. The hemisphere consists mainly of the 'taenioid' of lamellae that Bolk called the ansoparamedian lobe. In my comparative and ontogenetic studies, I came to the conclusion that these parts developed exclusively from the middle lobe. Also here in the mammalian cerebellum we find the above-mentioned principle, that the higher differentiation takes place mainly within the middle region. For the mammalian cerebellum, too, it holds that the marginal region, that is, the anterior and the posterior lobes, including the flocculi, behave very conservatively and show a moderate tendency to development, whereas the middle lobe shows the higher anatomical development. The really new parts all rise on the middle lobe. This forms the hemispheres, the main part of which is the lobus ansoparamedianus. Consequently *this is to be considered as the specific mammalian part of the cerebellum.* It appears within the vertebrate series simultaneously with the pons, the cerebro-pontine fibre systems and the pyramidal tract. We know that the cerebro-ponto-cerebellar connections end mainly in the cerebellar hemispheres. Thus the appearance of the ansoparamedian lobe synchronously with these important corticofugal fibre systems justifies the supposition that the cerebellar hemispheres are especially correlated with activities of the cerebral hemisphere. This assumption is perfectly correct, as will be explained more fully later. The

experimental and clinical evidence accumulated seems to show that the cerebellar hemispheres are mainly correlated with motor functions of the extremities or the higher motor activities activated by the pyramidal tract. A most valuable and interesting corroboration of my statement that the ansoparamedian lobe is to be considered as the specific mammalian part is given by Marion Hines, who, working in the Anatomical Department of the Johns Hopkins University, has recently shown that in Ornithorrhyncus no ansoparamedian lobe is to be found. This remarkable animal, which in so many structural respects reminds one of the birds, also has in fact a cerebellum of the avian type. The only difference is that it has a higher development of the floccular region.

A comparison between the human and the mammalian cerebellum shows that the former is developed in the same way as the mammalian, with the identical mutual interrelation between the different cerebellar parts. The specific characteristic feature of the human cerebellum is, in the first place, the extreme development of the hemispheres. This also is in conformity with the strong development of the pyramidal tract and the pons in human beings. This expansion of the hemispheres appears as an extreme elongation of the lamellae. Whereas in the majority of the mammals these form taenioid, more or less gyrant, tapes with a smaller type of lamellae, in the human cerebellum they are considerably elongated in a transverse direction. That gives to the human cerebellum its characteristic external pattern. For the rest, in studying the human cerebellum we need not resort to any hypothesis of any specific new parts within the organ in question. It is just the same as in the mammals. As regards more detailed questions, I will here say only that I came to the conclusion that the tonsil is homologous with the paramedian lobe, an interpretation that has been accepted by Jakob and others. The whole floccular region is in man very poorly developed. We find again the floccule of the mammal as the small floccule in man. The paraflocculus, or the strongly developed and characteristically curved tape of the lamellae that forms the most lateral parts in the mammalian cerebellum, has almost disappeared in man. We find it again as the minute accessory flocculus (Nebenflocculus of Henle). This regression of the floccular region is in my opinion to be correlated with the erect gait of the higher primates, including the human being.

My further studies of the cerebellar fibre systems corroborated my subdivision of the organ into three main parts or lobes. Of course it may be considered peculiar that special stress is laid upon the manner of subdividing such an organ as the cerebellum. In making his subdivision, a morphologist only gives expression to his personal phantasy, and he will never get rid of his subjectiveness in viewing the matter. Any subdivision therefore is really quite arbitrary. Nevertheless, I venture to assert that this way of dividing the organ is more in harmony with its inner structure than the earlier subdivisions. My further observations brought out important features of the internal organization, which impose a subdivision of at least three main parts.

In order to corroborate my proofs of the perfect uniformity in the external organization of the cerebellum in birds and in mammals, I undertook to investigate how far these external resemblances would also hold for the inner structure of the organ, and with this point in view it seemed advisable to examine the behaviour of some of the more important fibre tracts running to it. I chose the spino-cerebellar tracts or the fascicles of Gower and Flechsig. The ending of these tracts had been studied experimentally in mammals by many authors, but especially by Horsley and Salisbury MacNalty. In their short paper on this subject, however, I found some points that were obscure. I therefore studied by the Marchi method the spino-cerebellar tracts in cats, after these tracts had been damaged at different levels of the spinal cord. In this way I found that on reaching the cerebellum these tracts divide into two different fascicles that run to the anterior lobe and to the posterior lobe, whereas the middle lobe receives only a few fibres and for the most part only in its anterior portion—the lobulus simplex. Furthermore, I was able to confirm the statement, made by former investigators, that there is no regional representation of the different body regions within the areas of the end-stations of these fibres, since the fibres from the sacral spinal segments go exactly to the same region as those from the cervical. This fact undoubtedly also gives us some hints about the localization of the function within these parts. It favours the ideas that the function of these parts must be related to the body system as an entity, which is in perfect conformity with the findings of experimental physiologists, among whom may be mentioned Sherrington, Horsley, Loewenthal and Weed.

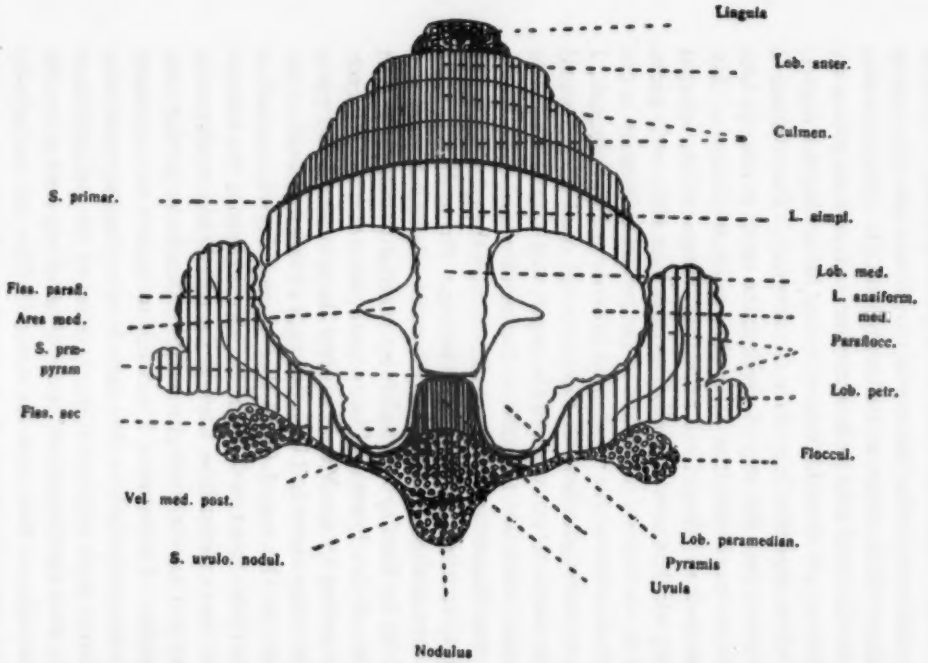


FIG. 3. DIAGRAM OF THE MAMMALIAN CEREBELLUM, THE CORTEX BEING SPREAD INTO ONE PLANE

Vertical lines mark the endings of the spino-cerebellar tracts; circles mark endings of direct fibres from the vestibular nerves. The surface of the cerebellar cortex is conceived of as being spread in one plane; the periphery of the figure corresponds to the base of the organ, that is, the parts situated in the immediate vicinity of the fourth ventricle and especially of the vestibular nuclei.

After experimental lesions of the spinal cord in pigeons, the endings of the spino-cerebellar tracts in the cerebellum were studied by the same method. There it could positively be shown that the end-stations of these fibres are to be found in regions of the cerebellar cortex corresponding exactly to those in the cat. Thus, the majority end in the anterior and the posterior lobes, while the middle lobe receives fibres only in its anterior part. This is undoubtedly a good corroboration of my statement that the cerebellum of the mammal and that of the bird must be considered as completely homologous organs. It is also a very important confirmation of the subdivision of the organ into three main lobes. Based originally on external morphological features of the intricate complex of lamellae, it also fits in with the internal make-up of the organ.

Of very fundamental significance is the fact that the spino-cerebellar fibres from the same body region, *e.g.*, the cervical segments of the spinal cord, on reaching the cerebellum, divide into two fascicles which are directed forward to the anterior and backward to the posterior part of the cerebellum, whereas the central region is free. We shall later have to consider the significance of this finding.

Next to the spino-cerebellar tracts the afferent vestibular fibres were taken up in my studies. Regarding the relations between the vestibular organ and nerve and the cerebellum, the literature of today shows great uncertainty. Until lately the prevailing idea was that the cerebellum was the main ganglion to the vestibular nerve and that it was functionally dominated by the nervus vestibularis (Sherrington). According to Bárány, all the vestibular reactions were elicited by way of the cerebellar cortex. Cajal in his comprehensive textbook on the histology of the central nervous system teaches that the fibres from the vestibular nerve run to the entire cerebellum. It was therefore a surprise that Magnus and de Kleijn could show that all labyrinthine vestibular reflexes can be elicited even after total ablation of the cerebellum. Magnus, who naturally does not deny in the intact animal an influence of the cerebellum on the labyrinthine reflexes, writes in his fine monograph, *Körperstellung:* "dass man endgültig mit der noch immer sehr verbreiteten Vorstellung brechen muss, nach welcher das Kleinhirn der Zentralapparat für die Labyrinthe sein soll." As a result of these conclusive experiments of Magnus and

de Kleijn the cerebellum has been to a certain extent dethroned from its rôle in connection with the vestibular organ.

Comparative anatomy teaches that the cerebellum develops in all vertebrates in the most intimate relationship with the vestibular nerves. In lower animals the vestibular relations are strongly developed. In Petromyzon the cerebellum forms a thin layer of cortex with typical Purkinje cells resting directly on the vestibular nuclei. In the fishes, according to Kappers, the vestibular cerebellar connections are richly represented. In amphibians and in reptiles the strong fibre bundles running from the vestibular nerve directly to the cerebellum can easily be demonstrated, as shown by my own studies of 1918. This intimate relation between the nervus vestibularis and cerebellum is conserved during the whole evolution. According to Van Hoevell the cerebellar nuclei are only derivatives of the vestibular.

But on the whole there is evidence showing that in the course of development among the afferent fibre bundles the vestibular apparatus loses its influence, and its place is taken by other important fibre tracts—the spino-cerebellar and cerebropontine tracts. Nevertheless, the strong vestibular influence on cerebellar function is shown by a great many anatomical facts. The cerebellopetal vestibular connections are widely distributed within the organ to the cerebellar nuclei and also to the cortex. To the basal lamellae, the lingula of the anterior lobe and the nodulus, uvula and flocculus of the posterior lobe, go direct fibres from the vestibular ganglia, as I was able to show conclusively by means of the Marchi method in the cat after experimental lesion of the vestibular nerve. These parts are located in the immediate vicinity of one another at the base of the cerebellum and in the proximity of the vestibular nuclei. These fibres running directly to the cerebellum from the vestibular ganglion of Scarpa undoubtedly form one of the oldest phylogenetic fibre tracts to the cerebellum. Those cerebellar regions may be assumed to be of an early phylogenetic age. They might be regarded as the phylogenetic calyx of the whole organ. Valuable support for the conceptions of the functional relations between the basal cerebellar regions and the vestibular organs is afforded by the experimental observations of Greggio. After excision of the vestibular peripheral organs in newborn pigeons, he found a defective development of the cerebellum,

particularly of its most posterior parts, that is, of its basal lamellae. Mesdag, in his ontogenetic studies of the brain of the fowl, has clearly demonstrated how direct vestibular fibres run only to the most posterior parts of the cerebellum. Groebbels has recently described how, after vestibular lesion in pigeons, he is able to trace by the Marchi method direct vestibular fibres to the anterior and to the posterior lobe, as indicated in my work. There can be no doubt as to the very intimate relation of the basal region of the cerebellum to the vestibular organs. And furthermore, in the distribution of the vestibular fibres to the cerebellum we also find ample support for the principle of the subdivision of the organ into three main lobes.

From my anatomical studies it was evident that the different afferent cerebellar fibres reached the cerebellum within limited regions of the cortex. I suggested calling the basal regions to which the direct vestibular fibres run the 'vestibular floor or story.' The regions where the spinocerebellar fibres end and which are situated in a way above the vestibular floor were called the 'spinal story.' The rest of the organ, *i.e.* the middle lobe including the hemispheres, forms the 'top floor.' It had been shown by several authors that the pontine fibres, *i.e.* the phylogenetically youngest afferent fibres, run mainly to the 'top floor' or the hemispheres. This therefore could also be spoken of as the 'cerebral floor.'

This conception does not pretend to be more than a crude schematic one. There undoubtedly exists an overlapping in the cerebellar cortex of the different afferent fibre systems. In spite of its crude schematic character it expresses succinctly, to my mind, not only the evolution of the cerebellar functions but also the functional organization of the organ. In my opinion it helps us more than any other representation to understand the functional integration of the afferent cerebellar impulses and thus also the question of the functional localization within the organ. That this conception of the different cerebellar stories has had a value is proved by the fact that, since I published my studies, this idea has been used by a great number of prominent authors on cerebellar anatomy and physiology (Kappers, Bremer, Judson Herrick, Miller, and others).

The phylogenetic continuity of the cerebella in the vertebrate phylum forms by no means an exception in the central nervous system.

In 1923 I started a comparative study of the diencephalon, using the same methods as in my cerebellar studies. In the map that the comparative anatomists of later decades have given of the central nervous system, the diencephalon has hitherto been only a white spot. Of the thalamus it must be confessed that there is hardly any other part of the central nervous system concerning which our knowledge is more diffuse and vague, in spite of the fact that the extant literature is enormous. This literature is very hard to utilize, largely because of the complete lack of an unanimous nomenclature. This conflicting chaotic nomenclature is undoubtedly due to a lack of anatomical understanding of the morphologic structures within the diencephalon. It is evident that this lack of anatomical insight has done much to hamper the endeavours of experimental physiology as well as of clinical neurology. We know that by these sciences the diencephalon is considered as being one of the most important centres for the nervous regulation of the most vital functions of the organism, especially the visceral or autonomic functions.

On the basis of these considerations I started my studies. I cannot here, of course, go into any details. I must refer to two small papers published by me in 1923 and 1924. I came to the conclusion that the main morphologic pattern of the thalamus as well of the hypothalamus is the same in reptiles and birds as in mammals. The principle of the phylogenetic continuity also holds for the intricate structures of the diencephalon. To my mind the morphological structures of the diencephalon in birds is strongly influenced by the enormous development of the tectum opticum, which corresponds to the anterior quadrigeminal body in mammals. We know that the latter is situated on the dorsal margin of the midbrain, its line of attachment to this running mainly horizontally. The avian tectum opticum occupies besides the dorsal almost the whole lateral side of the midbrain. Thus its lateral edge is situated on the ventrolateral margin of the midbrain. To the same extent, and probably for the same reasons, there has been a dislocation of the internal structures not only of the midbrain but also of the 'twixt brain. Thus the ventral margin of the optic thalamus proper, which in mammals in transverse sections runs horizontally, in birds takes an oblique direction. If from this general viewpoint the different thalamic structures of birds are com-

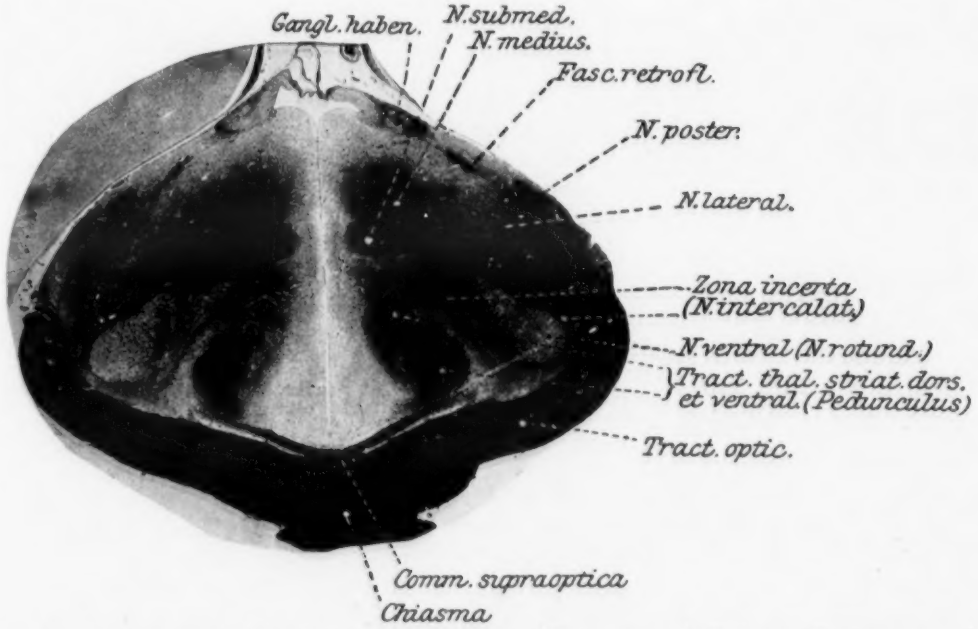


FIG. 4. TRANSVERSE SECTION OF THE 'TWIXT-BRAIN (DIENCEPHALON), THALAMUS OPTICUS AND HYPOTHALAMUS IN THE PENGUIN

Microphotograph. (Weigert-Pal preparation. Ingvar, 1922.)

pared with the mammalian thalamus, *it is evident that the thalamic nuclei of mammals are all to be found in the thalamus of birds.* The greatest difference is the stronger development of the lateral thalamic regions within the mammalian thalamus. But birds have already a primordium of the lateral nucleus. The greatest and most conspicuous formation within the avian thalamus is the nucleus rotundus. It corresponds to the nucleus ventralis C of Monakow. I have pointed out that these conclusions about the homologies are fully supported by the facts that we know about the fibre-connections of the nucleus rotundus in birds and the ventral thalamic nucleus in mammals. My statements of the complete homology to be established in the avian and mammalian diencephalon have in America been corroborated and further developed by Huber and Crossby. These authors must undoubtedly be considered as the best informed respecting the diencephalic structures at the present time. Kuhlenbeck in his textbook on the comparative anatomy of the central nervous system has also adopted the idea that the morphologic pattern of the diencephalon is identical throughout the vertebrate phylum.

This finding of the phylogenetic continuity of such an intricate formation as the diencephalon must be of the greatest theoretical value. It shows the remarkable conservatism of the structures of the central nervous system throughout evolution. In the two classes, the birds and the mammals, which in their external structures differ so markedly that they can be considered as real antipodes in evolution, the finding of an identical morphological pattern in so important and fundamental nervous structures as the diencephalon must be considered as especially striking. Whereas the external structures of the animals are characterized by a strong adaptation to the functional needs according to environment and behaviour, the morphological pattern of the central nervous system is evidently preserved throughout evolution. From this viewpoint the central nervous system is to be considered as the most basic morphologic principle of the animals. If we are entitled to speak about any fundamental anatomical centre of the organism, it should be looked for in the diencephalon.

The homologies of the thalamic structures of birds and of mammals gain in importance from the fact that the cerebral hemispheres in both these classes are anatomically so different. It has always been

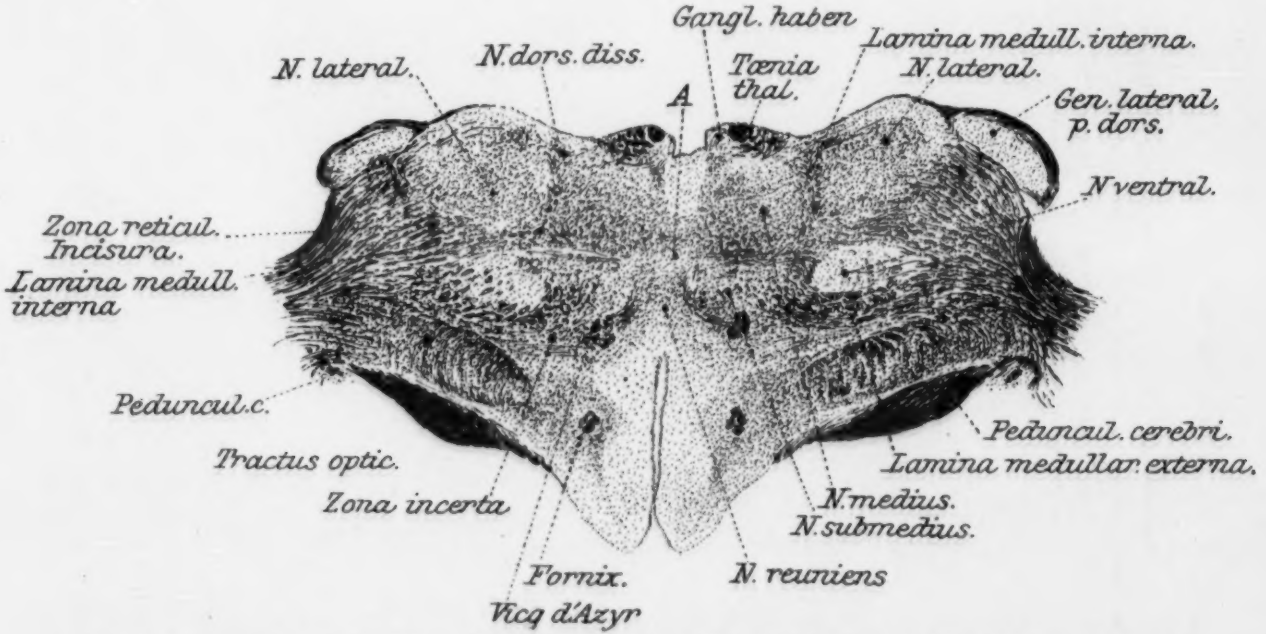


FIG. 5. TRANSVERSE SECTION OF 'TWIXT-BRAIN (DIENCEPHALON), THALAMUS OPTICUS AND HYPOTHALAMUS IN RABBIT

(Sketch after Weigert-Pal preparation. Ingvar, 1922.)

the general opinion among classical anatomists, and also among clinical neurologists, that the thalamic nuclei were, structurally as well as functionally, dependent upon the cerebral cortex. We know that the thalamus has been for a long time considered as a sort of functional connecting link (Schaltstation) between the cerebral hemisphere and the more caudal portions of the central nervous system. We know how men like Monakow and Nissl have for many years been looking for the cerebral parts of the optic thalamus (Gehirnanteile). The clinical literature has been influenced by the preconceived idea that there was a close anatomical relation between the cerebral hemisphere and the thalamic nuclei, so that each region of the cortex could be related to special thalamic nuclei. We know that Nissl spent his last years in laborious investigations on these questions. The fact that birds have the same thalamic nuclei as mammals, in spite of the fact that they have such a poorly developed cortex cerebri, shows in the first place the anatomical independence between the thalamic structures and the cerebral cortex. During the development of the cortex the thalamic structures are strongly influenced. Especially, the lateral nucleus is very definitely elaborated, but the thalamic nuclei are originally laid down and preserved without regard to the cortical formations. This notion cannot be without influence on the future studies of the morphological relations between the cerebral hemisphere and the diencephalic formations. It shows that the thalamus cannot be considered as a connecting link functionally, but must be a segment of the central nervous system with an important function of its own.

In birds the thalamic formations are anatomically very distinct. In the mammals the boundaries between the different thalamic nuclei are often diffuse, which has greatly complicated the anatomical subdivision of the thalamic structures by authors who have been working on the mammalian or the human thalamus only. The comparison with the birds shows that the fundamental cellular groups within the optic thalamus are relatively few. These comparative studies enable us to restrict the anatomical subdivisions and we shall be able to use only a few thalamic nuclei. This will be of great advantage especially to clinical neuro-anatomy, where the tendency of subdivision has actually been so exaggerated that it has obscured the

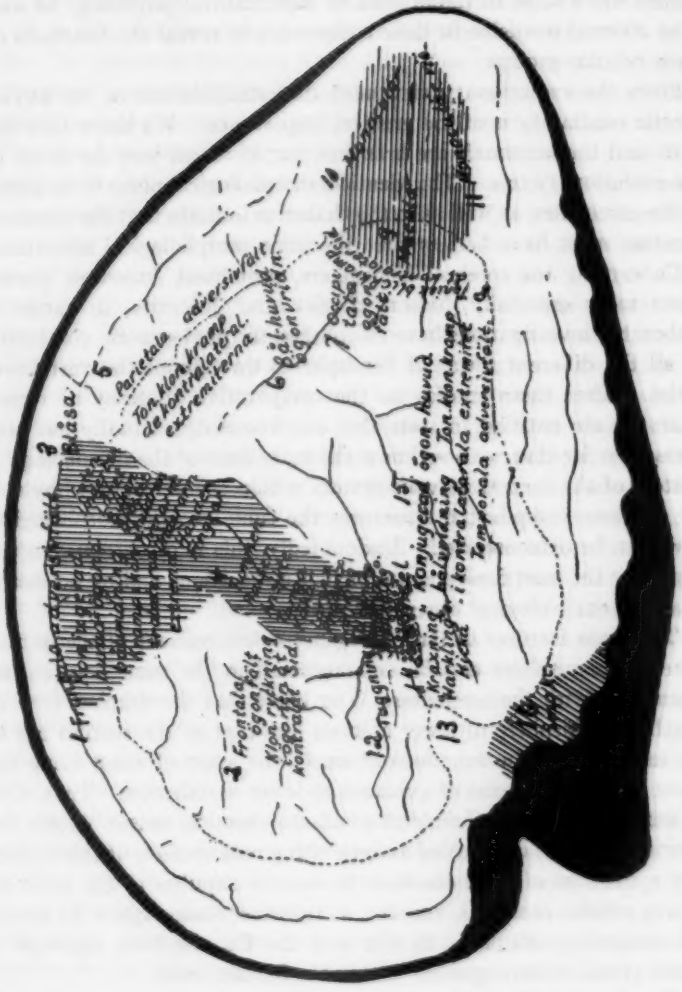
survey of these intricate regions. These comparative anatomical studies will also be of importance to experimental physiology as well as to internal medicine in their endeavours to reveal the functions of these cellular groups.

From the evolutionary viewpoint the establishment of the phylogenetic continuity is of the greatest importance. We know that the birds and the mammals are branches that diverged very far down in the evolutionary tree. The identical morphological plans to be found in the cerebellum as well as in the thalamus indicate that the common ancestor must have had *in nuce* the same morphological structures.

Concerning the cerebral hemisphere, prominent American anatomists more especially Judson Herrick and Johnston, in carefully elaborated investigations have established the phylogenetic continuity of all the different forms of hemispheres throughout the vertebrate series. After these studies on the comparative anatomy of recent years we are entitled to state that our knowledge actually has progressed so far that we now know the main lines of the morphological system of the central nervous system within the vertebrate phylum. In all these complicated structures the same general morphological laws can be demonstrated. Undoubtedly, this is of extreme importance for the most fundamental biological questions and by no means least for our biological conception of man.

The main features of the phylogenetic development of the human cerebral hemisphere can be demonstrated in the same way as has been done with the cerebellar. You know that the simplest form of cerebral hemisphere of lower animals like that of the reptiles has to do mostly with the functions of smell, the sense of smell being the most important means of guidance to lower vertebrates. Thus, that of smell seems to be the oldest of all the chemical senses. Even the human being has preserved an interesting reminiscence of this in that the epithelium of smell conducts its sensory impulses to the brain by direct cellular processes, and not, as the other sense organs, by means of connecting neurons. In this way the fila olfactoria represent a most primitive arrangement within the human brain.

The human hemisphere develops ontogenetically from a small vesicle into its final shape. If we conceive of this vesicle in the adult as being spread out into one plane, we shall find that the periphery


Pariet. adversivrörelse
Ton. klonkramp
Ögon-huvud
Frontala
Konjugerad ögon-huvudvridning
Occipitala
Temporala adversivrörelse

of this whole area is occupied by the rhinencephalon—*i.e.*, the regions endowed with the phylogenetically oldest smell-functions. Hence, it may be stated that the parts of the hemispheres that are endowed with the newer, more delicate functions arise exclusively within this frame of the oldest functions. The significance of this fact for the physiology of the hemisphere cannot be overestimated. The most important of the known centres of the hemisphere are developed inside the rhinencephalon according to their phylogenetic age. In the periphery, for instance, the motor bladder-centre is situated on the medial side of the hemisphere in the neighbourhood of the lobulus paramedia-

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FIG. 6. SCHEMATIC REPRESENTATION OF THE CEREBRAL CORTEX (PALLIUM) SPREAD OUT IN PLANE

The area outside the broken line shows the cortex on the medial aspect of the hemisphere. The black periphery denotes the olfactory pallium. Note the large frontal, temporal, and parietal adversive fields at the pallial margins, from which complex movements of the head, trunk, and extremities are elicitable. Note also that in the centre of the motor region the largest area is occupied by finger-movements, phylogenetically the last acquired.

The motor fields are given after Foerster (1926).

Key to Figure 6

1. Frontal adversive field, Conjugated head-eye and trunk turning, Spasm in contralateral limb
2. Frontal visual field, Clonic jerking of the eyes towards contralateral side
3. Bladder, Foot, Shank, Thigh, Abdomen, Chest, Shoulder, Upper arm, Forearm, Hand, Fingers
4. Thumb, Neck, Face, Tongue, Jaws, Larynx, Pharynx, Swallowing, Licking, Chewing, and Smacking
5. Parietal adversive field, Tonic-clonic spasm in contralateral limbs
6. Trunk-head-eye turning
7. Occipital visual fields
8. Tonic gaze spasm towards contralateral side
9. Macula

10 and 11. Monocular vision

12. Chewing
13. "Croaking," "Hawking," Hiccup
14. Hearing
15. Conjugated eye-head and trunk turning, Tonic and clonic spasm in contralateral limb, Temporal adversive field
16. Taste

nus. We do not know with exactitude the functions of the medial side of the hemisphere. I should be inclined to think that the sympathetic functions are to a great extent localized on the medial side. Then the centres of the different sense-organs follow in the peripheral regions, for instance, the centre of vision around the calcarine fissure and the gustatory centre in the region of the uncus or hippocampus. The most central regions, the parietal, the temporal, and the frontal areas are, as you know, considered to be endowed with the highest nervous functions, the so-called psychic.

If we consider motility as it can be elicited from the hemisphere, we have the area precentralis or gigantopyramidalis as a girdle crossing the central regions of the hemisphere. It is of important significance that the most central region of this motor area is to a great extent occupied by the centre for regulation of finger-movements. This is in complete accordance with the general conception of the hand- and finger-movements as the characteristic for the human. They represent the highest form of motility.

In recent investigations it has been shown that by using somewhat stronger electric currents definite motor phenomena can be elicited from extended regions within the periphery of the hemisphere. These are not individual movements of some single muscle group within the extremities, but very complex combined movements of the trunk, head and the extremities. On account of their general character they are often called adversion movements. These are of different types according to the different regions of the pallial periphery from which they are elicited.. Such global movements appear very often in epilepsy of the Jacksonian type and have proved to be of great value for local diagnosis, *e.g.* in cases of brain tumours. Quite recently, these types of movements have been thoroughly examined by Cecile and Oskar Vogt in monkeys. Foerster, in Breslau, has shown that the motor activities, which can be demonstrated in monkeys, correspond almost exactly to those that can be elicited from the human hemisphere. This is to my mind the best proof that these motor phenomena, which require stronger electric currents in order to be elicited, are not caused by spread of the current.

Moreover, for the motor function of the pallium, as well as for that of the cerebellum, the principle holds that the centre is the most

differentiated and has the most intricate and most highly developed functions. This way of demonstrating the structure and general plan of the human hemisphere has proved of great didactic value to me in my teaching. No other representation, so far as I know, gives the general plan of the hemisphere so clearly as this. No other representation so clearly shows how the hemisphere is built as a unit. Of course, it will also help us to understand how the hemisphere acts as a unit. As clinicians, we need all the help that we can obtain. It is outside the scope of this lecture to go into detailed questions concerning the cerebral hemisphere.

This representation will also be of value for the decision of some special questions of localization within the human hemisphere. For instance, the localization within the area striata of the fields for monocular vision is still a debatable subject. Some authors contend that it should be on the convexity of the hemisphere. There are a very few but conclusive observations supporting the supposition that it is localized within the medial side of the calcarine region of the hemisphere in the anterior part. According to this scheme it must lie on the medial side, *i.e.* on the most peripheral part of the area striata, since it represents the phylogenetically oldest function of the area striata.

It is evident that the establishment of the phylogenetic continuity of the central nervous system is of the greatest value to the biological sciences, and clinical neurology will also profit by it.

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STUDIES IN NEUROLOGY

II. On Cerebellar Function[1]

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In speaking to you about cerebellar function, the subject which I have chosen for my second lecture, I wish to emphasize at the outset that I am perfectly aware of the great difficulties associated with this problem. I also wish at once to remove any illusions that I am about to develop any final theory concerning the real nature of cerebellar function. In the recent literature on the physiology of the cerebellum, it has again and again been stated that the real function of this very interesting organ is unknown and that the question in the main is still unsolved. I must confess, however, that only to a certain extent do I agree with this statement, believing, as I do, that our knowledge of the structure of the organ is of importance for our understanding of its function. And I approach this question as a morphologist, because I am thoroughly convinced that the morphological knowledge that we now possess cannot be without importance for our conception of the function. I am perfectly aware of the many risks of educing function from structure, but, I believe that even the most skeptical physiologist will share the conviction that in our endeavors to understand the function of an organ we cannot afford to neglect the anatomical facts that are absolutely established. In the course of years my conviction has grown firmer and firmer that our anatomical knowledge gives us the most valuable hints about the cerebellar function. Our anatomical knowledge, to my mind, is in fairly close agreement with what we know from experimental physiology and clinical neurology of the different aspects of the cerebellar function.

The cerebellum develops in the whole vertebrate series in absolutely the same manner, according to the same general morphological prin-

[1] Second Herter lecture delivered at the Medical School of the Johns Hopkins University, November 4, 1927.

ciples. This uniformity is threefold. It concerns, in the first place, the external morphological features of the organ. In the second place, it holds for the microscopical structure of the cerebellar cortex, which in all animals preserves its typical three cell-layers, the most conspicuous of which is the Purkinje layer. In the third place, the cerebellum develops in all vertebrates in the immediate vicinity of, and with direct connections with, the vestibular nerves. It may be stated that our knowledge of the cerebellum simply culminates in these three facts. All these morphological uniformities can surely not be explained in any other way than in favour of the conception that the cerebellar function must be the same throughout the vertebrate phylum. Even more, for as the most primitive histological pattern of the cerebellar cortex is strictly maintained throughout the series, from the lowest to the highest, even including the human being, we are justified in concluding that the function of the cerebellar cortex must be a very fundamental, primitive one, as necessary to the life of man as to that of the lower animals. Otherwise, this great conservatism of the microscopic structures could hardly be explained. Otherwise it is impossible to understand how the instrument of the cerebellar function could be preserved throughout evolution.

In this connection a fourth great uniform morphological principle cannot well be omitted, *i.e.* the lack of any real sign of a histological differentiation within the cerebellar cortex in any animal, even in the human cerebellum. We know, for instance, that the cortex of the cerebral hemispheres shows a very marked histological differentiation into sharply delimited histological fields, as was established by Hammarberg, Campbell, Brodman and others. The Vogts in Berlin actually count about two hundred such cortical fields, many of which seem to have a very definite function. In striking contrast to this, in the cerebellar cortex there is a perfect histological uniformity. The differences hitherto shown concern only the number of the Purkinje cells, which may vary somewhat in different regions. As stated by Winkler, there are some slight differences in the myelo-architecture. The flocculus, for instance, has a type of myelo-architecture different from that of the rest of the organ. But these slight differences seem to appear in only the myelo-architecture. The cyto-architecture never shows any differentiation of different fields. Jacob finds in

preparations with silver impregnation no histological differences, even where he is able to show some with the Weigert-Pal method. Briefly, it may be stated that there is on the whole a perfect histological uniformity within the cerebellar cortex. That of course also points strongly in favour of a conception of a uniform function pervading all parts of the cortex of the organ in the human also. This I consider to be a fundamental working hypothesis of the greatest importance. If we are able definitely to show the function in any part of the cortex, this will be of the greatest importance for our understanding of the function in every other part of it. Before the time of comparative study of cerebellar morphology it was generally believed by physiologists that it was impossible to make direct comparisons between the symptoms elicited from this organ in different species. It seems to me that what we now know about the anatomical uniformities in the cerebellum absolutely justifies comparisons between the cerebellar symptoms described by experimental physiology and those found in the clinic. It was a great satisfaction to me to discuss this problem with the late Professor Magnus of Utrecht, one of the most exact workers on the physiology of the cerebellum. He told me that he too had become convinced that the cerebellar function in animals must in principle be universally the same all through, and he expressed his esteem for comparative morphology which especially had emphasized this point of view.

In the writings on cerebellar physiology, as well as in the clinical literature, there is much confusion, but this is to a large extent due to the luxurious use of an abundantly varying terminology. Every worker has his own terminology, but to the careful reader it becomes clear that the different symptoms described by the different authors in cerebellar diseases, or in experimental lesions, are all very similar. One feels sure that the phenomena which the different authors describe, each in his own manner, are the same, and nothing essential has so far been added since the days when Luciani gave his classical descriptions of cerebellar deficiency. The cerebellar symptoms are in fact experimentally very easy to elicit. The differences between the authors are mainly a matter of interpretation. However chaotic the literature has been, I dare to make the optimistic statement that of late years there has been a tendency to get out of the chaos and

adopt a more uniform conception. Whatever any one of them is inclined to think about the cerebellar symptoms as being caused by an asynergia or atonia and so forth, the very fact that the later authors of recent years try to look upon the different aspects of cerebellar symptomatology as expressions of only one fundamental disturbance, may undoubtedly be considered to be a step forward. In recent years, also, there seems to be an inclination to give to experimental physiology a predominance over the other different ways of getting at cerebellar function. Naturally, the experimenter is in a very privileged position, in that he is able to control the conditions for his observations much better than the clinician. Undoubtedly we owe the greatest advance in our recent knowledge to experimental physiology, even if the results have hitherto been mostly negative. On the other hand, we must not forget, as Walshe has pointed out, that for what we so far know positively about the organ we are for the most part indebted to clinical investigations. For instance, the fact that the cerebellum is involved only in motor and not at all in sensory functions, is certainly a very fundamental point that the clinic alone has made clear.

Ten years ago I formulated a theory about the cerebellar function. This was based chiefly on my anatomical findings respecting the great principle of uniformity that pervades the organ, but also on clinical observations of a certain number of cerebellar patients, and lastly on some experimental lesions. I concluded that the cerebellar regulation of the motor activities had to do with the regulation of the static and kinetic forces within the body masses so that their dynamic unity in movement would not be lost or disturbed. In this way I conceived of the cerebellum as regulating the muscular tension in the body masses in all motor activities, especially in abolishing and neutralizing the forces of gravity and inertia acting on the different parts of the body masses in a physical sense. In this way the cerebellum would be an organ of regulation for static or postural tone, or an organ of equilibrium in the wider sense of the word.

The main reasons for this conception of mine were based not only upon the great uniform principles established by my comparative studies, but upon the following considerations. The fact that the vestibular nerve sends direct fibres to the organ appears strongly to

support the theory. Of all afferent fibres to the cerebellar cortex, there is none that we know so well as the vestibular. For instance, we know with a fair degree of certainty that the adequate stimulus of this receptor comes from the movements and pressure of the endolymph and of the otoliths. In other words, if we translate this into physical terms, through the vestibular nerve are transmitted impulses of a static and kinetic nature. It seemed necessary to conceive of these vestibular fibres running to the cerebellar cortex as being involved in the regulation of muscular tone, as is the rest of the vestibular apparatus.

Another observation that strongly impressed me in favour of my general conception was the fact that in cases of cerebellar ataxia the impaired limbs behaved more or less like dead things attached to the rest of the body. This had been emphasized, especially by Holmes. It is a quite striking fact that the impaired extremities are much more affected by the force of gravity than the normal limbs, in spite of the absence of definite signs of paresis. "If either the arm or the leg be seized and shaken, it is found that the more distal segments of the affected limbs flop and swing about in an unnatural, inert manner, like the arms of a flail. While the oscillations of the normal limb are limited by the elastic tension of the muscles that are stretched, those of the affected limb can be felt to swing till the joints lock and their bony and ligamentous structures prevent their further movement. The affected arm swings about inertly as though it were attached to the shoulder only by a string" (André Thomas).

To my mind this is one of the most clean-cut symptoms in the cerebellar syndrome. It shows in a convincing way that the faculty of regulating or rather neutralizing the forces of gravity and inertia in cerebellar disease is lost. The general static and dynamic conditions are changed so that the afflicted members behave more or less like dead masses.

On these bases I explained the different aspects of the so-called cerebellar ataxia to be expressions of the disturbance of one fundamental function. Thus, the excessive range of movement in so-called hypermetria could be explained as deficiency in regulating the kinetic forces in the limbs at the end of the movement. It was consistent with this conception that hypermetria occurs especially in rapid movements or if a weight be tied to the affected limb. Adiadochokinesis in this

way is to be considered a natural consequence of hypermetria. Asynergia is also a natural consequence of this same fundamental disturbance consisting in the lack of fixation of the different members within a moving complex, for instance, in a limb.

My tentative theory about the cerebellar function was the natural fruit of anatomical and clinical studies. It proved to me to be a fruitful working hypothesis. Since I published my work in 1918, there has been a tendency in the literature to explain all the different features of the cerebellar deficiencies as expressions of one fundamental function. Two prominent English investigators, Walshe and Gordon Holmes, may especially be mentioned in this connection. Thus Walshe (1921) considers all the different cerebellar disorders to be caused by disturbance of postural tone. He writes:

> While it is scarcely necessary to go seriatim through all the disorders of voluntary movement observed in the subjects of cerebellar lesions, we may briefly take one or two of the most characteristic ones and consider them as possible results of postural atonia. Let us take for example proneness to fatigue, excessive range of movement (dysmetria) and oscillations or jerky variations of sustained movements, discontinuity of movement. They are found to be, without exception, inevitable results of loss of postural tone.

The most complete analysis of the cerebellar symptoms we owe to Gordon Holmes, and is to be found in his Croonian lectures. Having treated the different aspects of the cerebellar syndrome, deficient muscular elasticity, the occurrence and distribution of hypotonia, atonia, disturbances of attitude and of the tendon reflexes, cerebellar tremor, the rebound phenomenon, asthenia, increased fatigability, the typical disorders of movement, dysmetria, adiadochokinesis, disturbances of standing and gait, and nystagmus, he concludes his masterly analysis with the following words:

> The interpretations offered of the chief disturbances of function show that they can be explained by a small number of elementary disorders. The flaccidity and the lack of elasticity of the muscles are obviously due to the diminution or loss of that state of normal tension in them, which clinicians speak of as tone. The inability of the limbs to maintain attitudes in opposition to gravity or to the action of external forces, and the tremor or unsteadiness which develops under these influences, are a result of loss of that tonic component which stabilizes and sustains the voluntary contractions of the muscles. Hypotonia plays a large part in the disorders of

movement. Errors in range can be attributed to the same lack of tone in the antagonists, which should steady and moderate the action of the prime movers. The abnormalities in speech, too, can be explained by disturbances of the relations in posture and in movement of the separate organs concerned in it. In the inability to perform alternate movements, the adiadochokinesis, lack of fixation-tone in the muscles also plays a very large part. Finally, the only sensory disturbance that exists in cerebellar disease—that is, the inaccuracy in the comparison of weights—depends on the deficient tone in the muscles and not on a primary defect in any sensory quality.

But if all these elementary phenomena of cerebellar ataxia can be looked upon as a disturbance of postural tone necessary to conserve attitude, Holmes finds that the disturbance of coördination, especially delay and slowness in starting and effecting muscular contractions and relaxations, cannot be attributed wholly to atonia. He believes that the explanation of the disorders of gait and of the inaccurate coöperation of agonists and synergic muscles in other actions requires the assumption of a disturbance in the measure and time relations of the contractions of muscles that should work together harmoniously.

The conception of the cerebellar function held by André Thomas is focussed around the theory of anisosthenia, that is, a general disturbance of the tonic interrelation of the prime movers and the antagonists. A similar view has been recently adopted by Dusser de Barenne. His idea is shown by the use of the term "schizotonic ataxia" for the cerebellar disturbances. He emphasizes that the cerebellum is not the only part of the organism where the tonic functions are regulated. Dusser de Barenne, like Gordon Holmes, also finds that the cerebellum is not only related to the adjustment of tone, but that it also takes part in the regulation of the temporal and spatial side of the synergic collaboration in complex movements. Van Rhijnberk, after an extensive review of the literature on cerebellar physiology of the last ten years, concludes in the following words:

All the cerebellar symptoms experimental physiology has demonstrated and recorded, can, however chaotic they may appear, be related to the disturbance of one fundamental function, regulation of tone in the skeletal striped muscles. The gradation of tone is related to the conservation of the equilibrium of the body at rest or in motion, the posture of the body as a whole, as also of the different members of the body in their mutual interrelation, resting or in movement, and in all kind of motor activities. The function of the organ can be aptly expressed by a term of Sherrington's as "postural."

Miller, after reviewing the cerebellar physiology, ends in the following manner:

> To summarize briefly, we have in the cerebellum a series of intricate reflex centres, which, in response to streams of proprioceptive impulses from the labyrinths and muscles, emit finely graded impulses which assist, in a delicate manner, in sustaining or "regulating" the postural tone of the muscles in conformity with the attitudes and movements of the body.

Tilney and Pike in an experimental study have registered graphically the disturbance of movement after extended cerebellar lesions in cats and monkeys. They found that in normal motility there is not a reciprocal innervation in the sense of Sherrington. There was, according to these authors, no relaxation of the muscles checking the antagonist at the contraction of the prime movers, but a synchronous co-contraction of the antagonists. They speak of muscle groups, in which the contraction of the prime movers is accompanied by a synchronous contraction of the antagonists, as synergic units. After the lesions of the cerebellar hemispheres they found the functions of these synergic units to be disturbed. These disturbances were primarily in the nature of actual dissociations in the operation of the synergic units. The ratio of tension increment which is normally maintained between the dominant and the check muscle is entirely lost. The lack of regularity in the succession of the contractions within the unit was a marked feature of the dissociation. Further, the dissociation in time relation between the contractions of the muscles constituting the synergic units was equally conspicuous. "It is indeed the time element in the contraction of the check and dominant muscles, which constitutes the most striking feature of disorganization in the synergic unit, following on lesions of the lateral lobe of the cerebellum."

According to the theory of Tilney and Pike, the ataxia in cerebellar disease is thus mainly an asynergia, *i.e.* lack or disturbance of coöperation between the prime movers and their antagonists. This same general conception has been adopted by Weisenburg, another American author. The whole theory of the asynergia being the main feature in cerebellar ataxia is contradicted by the recent investigations of Pollack and Davis. They proved conclusively that the removal of the cerebellum does not affect the functional agonist-antagonist relations of the

muscular contractions in tonic and certain phasic reflexes of a decerebrate animal. Walshe and Holmes do not agree with the general idea that asynergia causes cerebellar disturbances. Following the work of Tilney and Pike in recent years, Holmes has repeatedly examined the relations of agonists and antagonists, and states that he has not been able to find definite disturbances in these relations.

I consider the asynergic symptoms to be secondary to the loss or disturbance of postural tone. This disturbance also means loss of fixation of the different parts of moving extremities. Such loss of fixation must necessarily disturb coöperation of the muscles within a moving complex, for instance, an extremity. Hence I consider the atonia to be the cause of the asynergia.

Spiegel has recently suggested that the cerebellum is interpolated in the central nervous mechanisms which effect the changes of the muscular tensions at the start of the movements. The cerebellum is, according to this author, one of the nervous centra in which static and kinetic impulses are integrated.

We find again and again in the literature how the general idea of cerebellar function veers toward the conception that it concerns the integration of the tonus in the different parts of the body musculature, as was concluded in my work of 1918. It is evident that this integration is necessary for the preservation of the dynamic unity of the various parts of the body.

In this way we find an explanation of the very striking anatomical fact that the cerebellum in its entirety with its bilaterality is an unpaired organ as compared with other important structures of the central nervous system, the cerebral hemispheres, the basal ganglia and so on. It is evident that an organ endowed with the function of preserving the dynamic unity of the body masses in the physical sense of the word could scarcely be a bilateral organ, since the body in itself forms a unit.

One of the most remarkable discoveries of later years in cerebellar physiology we owe to the experiments of Rademaker. Thanks to a highly developed technique he was able to remove the cerebellum totally from quite a number of cats and dogs that remained alive for months afterwards. The main result of this work was to show one thing definitely—that the regulation of the equilibrium

proper suffers very little from decerebellation. All the static reactions of the animals remain. The animals have a very definite faculty of equilibrium. He further denies emphatically that there is any loss of tone in his decerebellate animals. Notably, the so-called "Stützstonus" of the extremities is very strongly manifested.

Rademaker's animals are not able to stand still; on trying to do so they consistently perform irregular movements with the extremities. There is a conspicuous tremor of the head. The gait is very irregular and, in running, the movements of the extremities are quite disorderly, although the animals very seldom lose their equilibrium. In other words, there is a definite cerebellar ataxia in movement.

It seems to me to be of great importance that the irregular movements associated with the attempt to stand still cease immediately if a large fold of the dorsal skin is grasped, or if the animal is put on its back. This phenomenon might possibly be explained, according to the principles developed above, by the assumption that the irregularity in the movements of the extremities is caused by some sort of an insufficiency of the equilibratory functions. No function demands greater accuracy of the total equilibratory faculty than that of standing still. In these animals, if the trunk is in some way supported, the irregular movements cease immediately.

Rademaker further showed that the static reflexes were exaggerated in his animals. Furthermore, there was a loss of inhibition of the tonus distribution after a change in the position of different parts of the body, the head, the pelvis and the extremities. Even Rademaker, who denies an atonic component in cerebellar symptomatology, states that in these cases there is a marked disturbance of distribution of tone.

A few years ago I described a phenomenon that I called "spinal past-pointing." When a normal person has to direct his finger towards a fixed point in front of him with his eyes closed, he succeeds perfectly. But if he abducts his other arm up to the horizontal plane, the pointing arm deviates laterally from the fixed point. I called this phenomenon spinal past-pointing, because I thought that spinal mechanisms were mainly involved in it. This phenomenon, which has also been verified by Goldstein and Riese, must be explained as due to an influence on the tonus in the pointing arm caused by the

change in position of the other abducted arm. I have found it to be very irregular, and generally highly exaggerated in cases of cerebellar lesions. When Rademaker states that in his decerebellate animals there is a loss of inhibition of tonus distribution after change in the position of the different parts of the body, this is in fact identical with what I have found in cerebellar diseases as exaggerated spinal past-pointing. The exaggerated spinal past-pointing in cerebellar diseases is also in agreement with the conception of Goldstein, according to which the normal cerebellar innervation goes mainly to the flexors and the adductors of the extremities. On the whole, in my opinion, further observation of this phenomenon in cerebellar diseases is the most promising among our clinical tests, and further elaboration of it may provide a valuable bridge between clinical neurology and experimental physiology in this field.

Thus it seems to me that the results of Rademaker are not so opposed to the current ideas on the regulation of posture by the cerebellum as might be thought on first impression. Even the English authors, Holmes and Walshe, despite the experiments of Rademaker, still find their ideas of the cerebellum as serving to regulate postural tone to be defensible. Indeed they so expressed themselves in the recent symposium on the cerebellum at the Neurological Congress in London in 1927.

The clinical experience that the atonic phenomenon appears in cerebellar lesions is so strong that we cannot give up the idea that the cerebellum has some part in regulating postural tone. Rademaker's experiments have definitely shown that the equilibrium proper is maintained by nervous patterns laid down in the nervous system outside the cerebellum. But he has also shown that the cerebellum has an inhibitory, regulatory influence on the static reflexes. It also has an inhibitory influence on the tonus distribution following the interdependent changes in the different parts of the body. These two symptoms are in complete accordance with the general conception of the cerebellar function defended above.

Our actual knowledge of the cerebellum seems to favour the conception that this organ has a share in the finer regulation of the static and kinetic forces of the body masses in movements, even if the equilibrium proper is regulated by other parts of the central nervous sys-

tem. This conception is consistent with the fact that the cerebellar disturbances appear mainly in voluntary movements, as has been emphasized recently by Walshe. The voluntary movement means a changing of static and kinetic conditions of the body masses by cerebral impulses. In this way we find an explanation of the fact that that the cerebellar and the cerebral hemispheres in the vertebrate series seem to follow a perfectly parallel development.

If then so many facts, anatomical, physiological and clinical, support the conception of the cerebellar function as a uniform one, this of course does not exclude a topical localization of function. It must be assumed that the cortical function of a specific region is brought into play only, or mainly, from a certain region of the body, and that the function irradiates from a certain area in the cerebellar cortex by way of anatomical pathways only or mainly to special parts of the body. When we take into consideration our anatomical knowledge of the afferent fibre systems to the cerebellum, we shall find valuable arguments for the idea that there really is a definite distribution of functions within the cerebellar cortex.

In spite of the fact that all the endeavours of experimental physiology have failed definitely to show a localization of the function, we have proof that there really is a localization.

Undoubtedly the basal vestibular floor of the cerebellum in primates and in man does not play the same functional rôle as the spinal and the cerebral. In the course of evolution it has lost its functional importance to the same degree as the labyrinth has lost its importance as an organ of orientation for land-living animals. Nevertheless, the vestibular floor is of paramount importance to our understanding of the general organization of function within the cerebellum. Since parts of the vestibular nerve can be traced to this floor, it is not illogical to expect a symptomatology for lesions in this floor similar to that for lesions of the vestibular nerve itself. It was proved by the famous Luciani that after somewhat severe lesions of the cerebellum there appeared in the acute stage in the animals operated upon violent movements, which he called dynamic phenomena. After ablation of the vermis, Russel found that the animals fell backward and that this tendency was strongest when the posterior part of the vermis was removed. A few years ago I was able to show how violent was the

falling backwards after total ablation of the posterior lobe. Simonelli found the same, although he gave it a different interpretation.

In accord with Thomas and Müller, I consider it highly probable that the dynamic phenomena are vestibular symptoms elicited in the cerebellar cortex. Groebbels and other physiologists have also adopted this point of view in their work on the physiology of the avian cerebellum. Brunner in a review on vestibular function expresses the same opinion.

There are almost no receptors in the organism that we know so well as the labyrinth, especially after the thorough analysis made by Magnus and de Kleijn. The most prominent feature of the anatomy of the peripheral vestibular organs is the arrangement of the semicircular canals in the three planes of space. We also know that the clinical symptomatology of vestibular lesions is, as it were, connected with the different planes of space. Thus we find that stimulation of the horizontal canal results in nystagmus, mainly horizontal, past-pointing of the extremities in the horizontal plane, and lateropulsion of the body (Bárány). Any stimulation of the vertical canal produces vertical nystagmus, past-pointing in the vertical plane (upwards or downwards), and a tendency to fall backwards or forwards, that is, in the same vertical plane as the stimulated canal. There must therefore be a grouping of the vestibular impulses in the central nervous system in relation to these planes. Otherwise it would be impossible to explain the fact that the stimulation of a vertical canal, for instance, produces vertical nystagmus, vertical past-pointing, and falling in the same plane. The vestibular impulses acting on the mesencephalic motor apparatus for the eyes, as well as on the spinal motor apparatus for the extremities and the trunk, are grouped in relation to the planes of space, and this must necessarily also hold for the vestibular influence on the cerebellum. The vestibular innervation of the cerebellar cortex must, therefore, be arranged on the principles of the different spatial planes. A similar view has previously been adopted by Hughlings Jackson and by Ferrier and we also possess a few clinical observations which indicate that it is the case. Léri concludes that each semicircular canal must be connected with a special region of the cerebellar cortex. In later years this point of view has dominated the work of Ten Cate and Groebbels.

The latter has emphasied that the disturbances following a lesion of the anterior lobe are similar to those after a lesion of the frontal ampulla, and lesions of the posterior lobe are similar to those after destruction of the sagittal ampulla. Undoubtedly this idea deserves still further experimentation.

Our knowledge of cerebellar evolution justifies us in arguing that if it can be shown that the functional organization within the basal parts bears a relationship to the different planes of space, then this principle must also hold for the rest of the organ, because the entire organ is built within the frame of the vestibular floor and the histologi-

FIG. 7

A. Sagittal section of the cerebellum of the cat with the end-stations of the spinocerebellar fibres. (Schematic representation according to Ingvar.)

B. Sagittal section 2 mm. to the left of the median line of the cerebellum of the cat. The excitable zones are indicated by the heavy lines doubling the contour. (Figure taken from Bremer, 1924.)

cal structure is the same in the vestibular floor as in the rest. I have in my previous publications drawn attention to the vestibular floor as the most promising for investigations on cerebellar functions. The vestibular floor is located very deeply in the cerebellum and entirely hidden by the organ *in situ*. It is therefore mostly spared in the experiments, owing to technical difficulties. I do not hesitate to state that these basal regions of the cerebellum really contain the key to an understanding of the whole organ.

I have already mentioned that the spinocerebellar fibres end in the anterior and posterior lobes within limited areas. That this really has a significance we now know from the studies of the Belgian physiologist Frédéric Bremer (1922). He showed, in Sherrington's labora-

tory, that by stimulation of the cortex with weak electric currents an inhibition of the extensors of the extremities could be elicited from these regions. Bremer finds that the boundaries of these excitable areas are very definite. They correspond exactly to those found by Salisbury McNalty, Horsley, and myself. The anterior lobe receives the majority of these fibres. Here also the strongest effect of inhibition on the extensors could be elicited. In the middle lobe, which is free from spinocerebellar endings, there is no such effect but then again in the posterior lobe the same inhibition is found, exactly in the pyramis, the only part of the lobe where only spinocerebellar fibres end.

Bremer, in 1924, extended his studies to the avian cerebellum. In pigeons he found, by stimulation of the anterior lobe (of my nomenclature), exactly the same effect within a limited area, corresponding to the lamellae where in birds I had indicated that the majority of the spinocerebellar fibres end. The middle lobe showed itself to be perfectly inexcitable. The posterior lobe he was not able to investigate from this standpoint because of its hidden position. Bremer emphasizes that the analogy of the symptomatology after lesions of the anterior and the middle lobes within the cerebellum of birds and mammals affords a strong corroboration of my views favouring the complete homology of these organs.

Undoubtedly it can be stated that these physiological findings which corroborate the above-mentioned anatomical findings of the spinocerebellar fibre-tracts ending in two very definite regions of the cerebellar cortex constitute the most important evidence of a localization or distribution of the cerebellar function. It is only rarely that anatomical evidence is in such conformity with experimental physiology. When it happens we may feel convinced that we have reached some sort of fundamental knowledge. I therefore venture to consider the above findings as good starting-points for further studies on the extremely debated question of functional localization within the cerebellum. Concerning this question Miller (1926) maintained that only a theory that would attach due importance to the sites of termination of the various categories of the cerebellopetal fibres, as determined by Ingvar, is likely to solve the intricate question of localization within this organ.

The vestibular and the spinal floor form together the largest part of the cerebellar vermis. They form especially the larger parts of the anterior and posterior lobes, which phylogenetically showed a great conservatism. It seems reasonable to conclude that the parts which changed so little during evolution should represent a fundamental function. This is in accordance with the clinical experience that lesions of the vermis are always followed by graver and more global motor disturbances than lesions of the hemispheres.

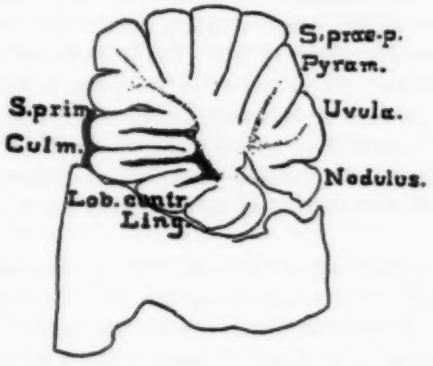

FIG. 8. END-STATIONS OF THE SPINO-CEREBELLAR FIBRES IN THE CEREBELLAR CORTEX IN THE PIGEON ACCORDING TO INGVAR. SAGITTAL SECTION OF A BRAIN TREATED BY THE MARCHI METHOD.

The excitable zone of the anterior lobe is marked by Bremer by a heavy line. (Figure taken from Bremer.)

Furthermore, the fact that it can be stated categorically that the parts of the vermis receive the spinocerebellar fibres which, according to Bing and Marburg, originate from all segments within the spinal cord that are not segmentally represented within the cerebellar cortex, makes it highly probable that these regions have a function correlated with all spinal segments, *i.e.* the body or organism as a whole. This is also in accordance with evidence collected by experimental physiology and clinical neurology.

Bolk concluded, from his anatomical studies, that the anterior lobe was connected with the muscular functions of the head, the face,

the tongue, larynx, etc., whereas the posterior lobe (according to my nomenclature) was related to those of the trunk, especially the tail and perineum. My studies on the fibre connections cast doubt upon this system of localization. Neither anatomically nor physiologically is there any evidence of any regional representation of the body segments within the cerebellar vermis.

Clinical symptoms favour the opinion that the principle underlying the structural organization in the vermis is regulation of the muscular activities of the organism as a whole. The deficiency symptoms after vermis lesions often manifest themselves as impairment of equilibrium or a tendency to fall. The latter is very often mentioned in the literature. Nothnagel refers to it and states that it usually occurs in a forward or backward direction. Adler, Bruns, Stewart, Holmes, and others have reported several cases. According to some authors a lesion in the posterior part of the cerebellum produces falling backwards while a lesion of the anterior portion is followed by a falling forwards.

It is noteworthy that a sceptic on cerebellar localization like Gordon Holmes writes: "Certain facts indicate that there may be a further localization of function within the human vermis. I have, for example, observed a tendency to stagger backwards, in tumours and other lesions of its posterior portion, and a falling forwards in one case, at least, of tumour in its anterior part."

As regards the lesions of the lateral regions of the cerebellum there has for a long time been agreement among clinicians that they give a falling sidewards, mostly to the homolateral side of the lesion. In 1923 I formulated my clinical experience somewhat as follows: When lesions involve the vermis, the forced movements or falling take place around a frontal axis, mostly backwards, while lesions of the lateral parts, the hemispheres of the cerebellum, give rise to forced movements or falling in the frontal plane around a sagittal axis towards the sides.

I believe this statement to be correct. On the other hand, we must not forget the extreme difficulties which clinical neurology is encountering in these fields. We must remember that the cerebellar lesion mostly involves rather extensive parts of the organ. Tumours dislocate the other parts of the organ, exerting a pressure upon them. In

hemorrhages and in abscesses there is a copious oedema in the cerebellar substance. Any process encroaching upon this limited space within the posterior fossa of the skull also exerts a pressure on its total content. We know from autopsies how common are the dislocations, especially of the bulb, in diseases of the cerebellum. These also mean a pressure on the sensitive vestibular nuclei, which complicates the symptomatology not a little.

Concerning the hemispheres there have been made, as we know, a considerable number of experiments in attempts to reveal the localization of function within them. We know that the hemispheres (according to the nomenclature of Bolk) consist of the ansiform lobe and the paramedian lobe. Bolk concluded from his anatomical studies that the first part of the ansiform lobe, the crus primum, was related to the function of the foreleg, whereas the hinderpart, the crus secundum and the paramedian lobe, was related to the hindleg. At first there appeared several papers (van Rhijnberk, and others) which seemed to corroborate Bolk's ideas. In later years, however, the statements on this topic in the literature of experimental physiology are rather conflicting. It is impossible to gain from them a definite idea as to whether there is a definite foreleg and hindleg centre. We must confess that there is nothing shown with any degree of certainty respecting localization in the hemispheres. One thing seems to be definitely established, and that is the statement of Luciani, that lesions in the hemispheres produce motor disturbances in the homolateral extremities.

Mills and Weisenburg many years ago proposed centres for the arm and leg in the human cerebellum. André Thomas states that the centres for the arm and the leg in the human cerebellum are arranged in the same manner as in cats and dogs, the anterior part of the lobulus ansiformis being related to the arm and the posterior to the leg. That the arm is related to the anterior part of the ansiform lobe is shown by a case of cerebellar abscess described by Thomas, in which the symptoms were limited to the right arm, though the seriousness of the condition did not permit of a careful examination. After death an abscess was found in the substance of the right superior semilunar lobe, but the whole hemisphere seems to have suffered, since it was oedematous and more voluminous than the left. The fact that the

symptoms principally affected the arm gives a certain importance to the case. It speaks in favour of an arm-centre in the lobus semilunaris superior.

In a recent publication Thomas gives several instances of cerebellar lesions in which the symptoms appeared mainly in the upper or the lower limb. Such observations indicate that there must be a strict localization for these regions of the body within the cerebellum. Unfortunately the author had no opportunity of correlating his clinical observations with the anatomical lesions, and these cases have therefore only restricted importance.

Rothman mentions a case in which he was able to diagnose an otogenic cerebellar abscess in "the posterior part of the hemisphere" owing to the fact that the ataxia had started in the leg. Marburg finds that tumours of the ponto-cerebellar angle produce more marked symptoms in the arm than in the leg. On the whole, the statements of localization within the human cerebellum may be characterized as less definite.

The first observation of cerebellar disturbances confined almost entirely to the leg, in which the clinical observation has been strictly confirmed by the autopsy, was first published by me, in 1919. It is strongly in favour of a localization in the hemisphere of the human cerebellum.

Case 1. The patient was a janitor aged fifty-one years, who, after difficulties for some months with defecation, tenesmus and diarrhoea, was admitted to the medical clinic (Karl Petrén) at the University in Lund with rectal cancer that was considered inoperable. The patient had vomiting attacks and headaches that made some intracranial complication very probable. On examination the only positive neurological symptom that could be demonstrated was a motor disturbance in the right leg. The finger-nose test was carried out promptly on both sides. But the knee-heel test was accurate only on the left side, being much disturbed on the right. The patient threw the right heel roughly and clumsily beyond the left patella up to about the middle of the left thigh and on moving the right foot back to a spot marked by the examiner's finger on the lower part of the left leg, the spot was also passed, though not so far. With the right leg this test was always repeated with the same inaccuracy. There was a marked inward past-pointing in the same leg. Only a slight adiadokinesis on rapid pronation and supination of the right arm was seen; no disturbance in the left arm was observed. The patient was examined for a week with the same constant finding. The knee-heel test was constantly performed

with the same apparent excess of motor innervation as before, the right foot being thrown far above the left knee. The patient gradually became weaker and died.

Owing to the cerebral symptoms a cranial tumour was suspected, probably a metastasis from the rectal neoplasm. Since the clinical disturbances were of cerebellar nature, this tumour was localized in the cerebellum, and as the symptoms affected the right leg only, the tumour was placed in the right leg-center of the right cerebellar hemisphere. The existence of a leg-center in the human cerebellum had never been demonstrated, but from the analogy with the mammalian cerebellum it was assumed that it must lie in the lobulus biventer. The autopsy completely verified the diagnosis. In the right biventral lobe a tumour was found. Its greatest horizontal diameter was 5 cm., the vertical diameter was 4 cm. Microscopical examination showed it to be a metastasis from the rectal cancer. It was situated entirely within the lobulus biventer, occupying the medial mass of this lobule on the inferior surface of the hemisphere and was covered by only a thin layer of cortex until the fossa transversa (Ziehen) and flocculus were reached. It was sharply limited by the deep fissure that separates the lobulus gracilis from the lobulus biventer and thence spread laterally and backwards into the substance of the lobulus biventer to the region where the lower anterior surface of the hemisphere borders on the lower posterior surface. The white matter, as could be seen on transverse sections, was not involved by the tumour. The main mass was free but displaced upwards and backwards. The dentate nucleus had also escaped, but its central foldings had been pushed somewhat dorsally, and its hilus was compressed.

So far as I know, this case is the first clean-cut one that indisputably shows the presence of a definite leg-center in the human cerebellum, situated on the posteroinferior surface of the hemisphere. Since that time, I have had my attention directed to this question, and I have been able to make several observations in other cases that corroborate this opinion.

Case 2. A short time ago I examined in the pediatric clinic of Lund (Prof. af Klercker) a child, ten years of age, who for the preceding eight months had suffered from headache and vomiting, and had the symptoms of increased intracranial pressure with bilateral choked discs. Almost the only neurological symptoms shown by the patient were those of cerebellar ataxia, these being solely in the left arm and leg and most pronounced in the arm, the leg showing only slight ataxia. There was a strong disturbance of the diadochokinesis on the left arm, whereas the knee-heel test was performed with only slight inaccuracy. On the strength of this finding I suggested that the patient was suffering from a cerebellar tumour of the left hemisphere. The discrepancy of the ataxia of the arm and leg indicated that according to the above developed principles the tumour should be situated on the upper surface of the hemisphere. At the operation a gliomatous cyst was found which occupied the upper surface of the organ, whereas the inferior surface was free. Sections of the organ showed that the infiltration of the tumour had spared the lamellae of the biventral lobe as well as those of the tonsil.

Case 3. H. B., forty-two years of age (medical clinic, Lund). Admitted to the clinic the first time December 18, 1925. (Record 1925/1926). The patient had always been healthy until the summer of 1925, when he began to suffer from a feeling of uncertainty and clumsiness in the left leg which would not obey. In addition, he complained of dizziness and slight headache. On admission to the clinic the first time, there were bilateral choked discs. There was no opisthotonus, no tenderness on extreme movements of the neck. The neurological examination showed very few abnormal symptoms. Nystagmus to the right, mainly horizontal, but with a rotatory component. There were bilateral choked discs. Tendon and periosteal reflexes active but equal on both sides. No symptoms of paresis. When the patient stood with closed eyes, he constantly showed a tendency to fall backwards. Gait with open eyes of somewhat spastic type, very uncertain with closed eyes.

On examination of the cerebellar functions the most striking phenomenon was the intense disturbance of the knee-heel test performed with the left heel on the right knee, whereas the same test with the right heel on the left knee was performed accurately. There was no disturbance of the finger-nose test either on the left or the right side. Sometimes a slight adiadochokinesis appeared in the left arm, in the right there was none. The patient was examined several times, attention being directed especially to the disturbances of the knee-heel and the finger-nose tests. There was sometimes also a slight tremor in the right leg, when it was put on the left knee. But when the left heel was put on the right knee there was often seen a coarse oscillation of this left foot, lasting for several seconds. These were intensified if the patient pressed the left heel against the knee. When the patient had to perform the knee-heel test with the left leg, the left foot was thrown far above the right knee; this same disturbance was much less marked if the test was performed with the right foot.

January 4, 1926. The knee-heel test shows the same uncertainty with the left heel on the right leg; with the right it is performed fairly accurately. The finger-nose test on both sides is performed. There is adiadochokinesis on the left side.

February 10, 1926. There is a marked adiadochokinesis of the left hand. Finger-nose test normal on the left side. The knee-heel test with the left knee on the right knee is performed with the same oscillations as before. Perhaps these oscillations are now somewhat marked. These tests performed with the right arm and leg show no disturbances.

The patient was treated with x-rays over the posterior fossa of the skull on the left side.

As the choked discs remained and were considered to be a danger to the vision of the patient, it was decided to advise operation. The patient was admitted to the surgical clinic on April 22, 1926. It was supposed *that he was suffering from a tumour in the left cerebellar hemisphere. As the ataxic phenomena constantly were demonstrated to be predominant in the left leg, whereas the left arm was almost free, it was supposed that this tumour was situated on the inferior surface of the left hemisphere.* The operation was performed by Professor Gustaf Petrén. The posterior fossa was opened

bilaterally. After incision of the dura it could be demonstrated that there was no tumour emanating from the acoustic nerve. Considerable bleeding then made it necessary to discontinue the operation. Palpation of the posterior parts of the left hemisphere gave no signs of a tumour.

After the operation the patient at first showed considerable subjective improvement. The headache and the protrusion of the choked discs disappeared. The above mentioned objective symptoms remained. Later the condition of the patient again grew worse. He developed a strong general cerebellar ataxia in spite of the renewed x-ray treatments. The gait became very disturbed, the left leg especially did not obey. He also developed cerebellar speech. There was finally a grave disturbance of the knee-heel and the finger-nose tests on both sides. In the final stages he had a marked paresis of the right arm and the leg.

He died Jan. 3, 1928, in the medical clinic. At the autopsy (by Docent Lindau) a large tumour was found at the left pons angle. The tumour, which microscopically was a meningeoma, had dislocated the pons and the medulla oblongata considerably to the right. As a result of the pressure of the tumour the left side of the pons was concave. The anterior part of the tumour was extracerebellar, but the posterior three-fourths had taken the place of the larger part of the left cerebellar hemisphere. Of this only the semilunar lobes remained besides the upper vermis and the parts of the white substance situated close to the fourth ventricle. The tumour was sharply limited from the cerebellar tissue. Docent Lindau finishes his record: "In all probability *the tumour had originated in the dura of the base of the skull on the inferior anterior side of the cerebellum.*"

Thus, as far could be judged from the autopsy, the tumour had emanated from the inferior side of the cerebellum. At the operation eighteen months before the death of the patient it was suggested that in view of the predominance of the ataxic phenomena in the left leg the tumour should be situated on the inferior surface of the left hemisphere. The autopsy findings show that the suggestion made at operation was correct. It is natural that a tumour with such an origin in its early stages must have exerted pressure, especially on the inferior surface of the hemisphere, where the leg centre is supposed to be situated in the lobulus biventer.

In view of our experience, then, I hold the topical representation of the arm and leg within the hemispheres of the human cerebellum to be firmly established. It is in conformity with data gained from experimental physiology. On the other hand, with regard to our general conception of the cerebellar function as mainly regulating the postural tone of the body masses, it is impossible to conceive of a strictly limited representation of the arm or leg motility within the cerebellar cortex. Since they are attached to the organism as appendices, where the motor activity in one segment has an influence on the static and dynamic conditions in other parts of the organism, or

the organism as a whole, then the arm or leg movements cannot be limited exclusively to a definite cluster of lamellae. There can only be some sort of prevalence of topical representation of function in the sense of Rossi, and this only within the most recent parts of the organ. What I want to emphasize is that this prevalence of representation of function in the human cerebellar hemisphere really has a clinical value. Gordon Holmes writes on the same question: "In a certain number of cases, however, the one limb seemed to be relatively more affected than the other, the leg being more involved by caudal and mesial lesions and the arm by more anterior." He adds: "But this localization is so indefinite that I would not regard it as a trustworthy guide in the diagnosis of a small lesion, such as a cortical tumour." The cases cited above show that Gordon Holmes is too skeptical on this point. It is true that very often the disturbances in the arm and in the leg are about equally pronounced, but on the other hand if there really is a distinct discrepancy in the ataxic phenomena, then it justifies us in attaching due attention to it. This fact will give valuable hints to surgeons in their search for tumours or abscesses within the cerebellar hemisphere. We must remember that although the neurologists may not be able to give a positive diagnosis of the exact location of the lesion, any hint as to the direction in which it is to be looked for is helpful. The clinical value of this observation is augmented by the simple way of testing these points. The old method of finger-nose and knee-heel test and the adiadochokinesis are sufficient. The former, especially, can be performed by the patients even if they are weak or debilitated. Even for patients in the final stages these tests can therefore be used, a fact that greatly increases their clinical applicability and value.

This short survey which may contain some of the most important ideas about the cerebellar syndrome indicates how strongly uniform are the tendencies in the recent literature on cerebellar function. For the most part, disturbances of postural tone are placed in the foreground as the most conspicuous phenomena in the cerebellar syndromes. There is a general agreement that this viewpoint enables us to consider at least all the most important sides of cerebellar ataxia from one single point of view. In this way we shall also be able to understand the great morphological conservatism of the organ in the

process of evolution. We understand that the cerebellar cortex is the same all through the phylum; it follows that preservation or rather exact integration of postural tone must be of equal importance to all vertebrates.

Anyhow, we must confess that the formula of the cerebellar function has not yet been definitively found and that much more work remains to be done. The experimental investigations being conducted along the lines indicated more particularly by Magnus and his school seem to be most promising in this field. Rademaker, Pollock and Davis have already presented valuable contributions in this direction.

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See also the bibliography of the first lecture.

ON THE PATHOGENESIS OF THE ARGYLL-ROBERTSON PHENOMENON[1]

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The reflex immobilization of the pupil, or the Argyll-Robertson phenomenon as it is called after its British discoverer, belongs as we all know to the most important of our clinical symptoms and is of equal importance to the opthalmologist, the neurologist, the syphilologist and the internist.

As a clinical conception the abolition of the pupillary reflex is one of our best known and most accurately described symptoms. The clinical literature on it is, naturally, enormous. But of the pathophysiology of the Argyll-Robertson pupil we know almost nothing; at least nothing with certainty, in spite of all the discussions contained in the literature.

The reflex stiffness of the pupil occurs, as is well known, especially in syphilitic diseases of the nervous system. Among etiologic factors tabes and general paresis play the most important rôle. The Argyll-Robertson sign appears in these diseases, very often as a premonitory symptom many years before any other morbid manifestations. The finding of this symptom suggests, at once, a syphilitic etiology. Experienced clinicians, as Bumke, still maintain that it simply proves the presence of syphilis in the central nervous system. Generally it is thought that syphilitic meningitis does not so often give the symptom as the real so-called metaluetic diseases, tabes and paresis. But it must not be forgotten that the metaluetic diseases are always associated with meningitic processes. There are several cases described (Nonne and others) where the Argyll-Robertson pupil has persisted for many years after a syphilitic meningitis, but where the anatomical investigation did not reveal any changes whatsoever in the central nervous system (Nonne, in a case examined anatomically

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by Wohlwill, Jelliffe, and others). Cases of typical reflex stiffness of the pupils, which for years show only this isolated symptom, and where all other clinical tests, including the serological, exhibit no abnormal conditions, are to be regarded as rather common. Sometimes it may be difficult to decide whether such cases should be regarded as luetic or metaluetic processes. But this question is losing some of its importance owing to the fact that in the light of newer anatomical investigations (Hassin, Richter, and others) it has been proved that in genuine tabes also there are real meningitic changes, even if the question of the relation of these meningitic processes to the tabetic degenerations is not yet settled (Spielmeyer).

It can be stated as a most reliable statistical fact that the Argyll-Robertson pupil occurs almost exclusively in syphilitic lesions of the central nervous system. This clinical fact is the more striking if one realizes that other organic nervous diseases only very seldom produce this sign. From this alone it must be concluded that the syphilitic poison has a special predilection for the physical substratum of the light reflex. This has usually been conceived of as a predilection of the syphilitic toxin for the pupillary pathways (Strümpell, Nonne, Behr, Bumke, Spiegel). In the present paper it will be shown that it is not necessary to have recourse to a hypothesis of any toxic predilection. It will be maintained that the well known pathological changes of the cerebral meninges and marginal degenerations in luetic and metaluetic diseases are apt to produce the pupillary disturbances, because the pupillary pathways run in immediate contact with the meninges on the very surface of the basal brain regions.

Among organic nervous diseases in which the reflex pupillary stiffness occurs, disseminated sclerosis is also mentioned (Marburg, Nonne, Lewandowsky). But we know that in this disease this symptom is not only atypical but is a great rarity even in the most advanced stages. This clinical notion gains in importance if correlated with the fact that in advanced cases this disease is marked by numerous inflammatory foci, disseminated over the whole nervous system. We may conclude from this that disseminated sclerosis, in spite of its wide anatomical extension in the brain, in the majority of cases shows a tendency to spare the pupillary apparatus. The polioencephalitis superior of Wernicke is said to cause the Argyll-

Robertson pupil. This seems plausible, as we know that this disease is characterized by destructive hemorrhagic lesions in the region of the oculomotor nucleus.

In later years epidemic encephalitis seemed to become an important concurrent to syphilis in causing the reflex stiffness of the pupil. To be sure, pupillary disturbances are among the most common of all symptoms in the acute stage of this disease. This clinical fact also receives its logical explanation from what we know of the anatomical extension of the morbid process in epidemic encephalitis. It has been shown definitely by numerous careful investigations, that in the acute stage we have encephalo-meningitic processes in the region of the oculomotor nucleus, the third ventricle, the Sylvian aqueduct, and elsewhere. It is no wonder that the nucleus of the pupillary sphincter and its pathways also are often implicated in them. But we also know that, when compared with the lesions in poliomyelitis (the Heine-Medin disease), the changes are generally less destructive, and as would naturally follow, we find that the pupillary disturbances in epidemic encephalitis are not permanent. Behr emphasizes, as a general peculiarity of the encephalitic pupillary symptoms, their great instability. In severe cases there are signs of intense irritation of the sphincter pupillae with marked myosis, which may change into a mydriasis. In this disease different kinds of intricate pupillary disturbances occur, and we have even the Argyll-Robertson pupil, but according to Behr this last in its genuine form appears to be a rarity.

Among toxic agents causing abolition of the light reflex, severe chronic alcoholism is mentioned (Nonne), and an occasional case is associated with diabetes mellitus and sulphide poisoning. In these disorders the Argyll-Robertson pupil is usually bilateral. Hence we must assume that these toxins possess a special affinity for the pupillomotor pathways.

In addition, it should be mentioned that in isolated cases severe traumatism of the skull is followed by a genuine reflex immobility (Axenfeld, Guillain, Wick, Finkelnburg and others). The pathogenesis of this traumatic abolition of the light reflex is not understood. Tumours and pathological processes in the region of the anterior corpora quadrigemina may also produce an Argyll-Robertson pupil.

This is in accordance with our knowledge of the course of the pupillomotor pathways in the anterior arm of the corpora quadrigemina (experiments of Karplus and Kreidl).

Such are the most important causes of the abolition of the pupillary light reflex. It is striking, that all other organic diseases of the central nervous system, compared with syphilis, play a very insignificant part. This fact in itself, to my mind, is not without importance for gaining an insight into the pathogenetic mechanism of the Argyll-Robertson phenomenon, as will be developed later.

The syphilitic diseases do not merely predispose as no others to the occurrence of the reflex stiffness, but this symptom appears in these diseases in quite a typical form. In the first place, it is characteristic that the stiffness begins gradually as a simple sluggishness of the light reflex. In the initial stage contraction of the pupil is merely reduced and retarded. This irregularity, as is well known, in the early stages is limited to one or several distinct spots on the pupillary circumference; in course of time it involves the whole pupillary margin. As a result of the irregular progress of the process, the pupil often loses its normal roundness and becomes angular. Gradually it narrows and becomes myotic. At the time that the reflex immobility becomes complete, a pronounced myosis is fully developed.

Of 56 patients with a fully developed Argyll-Robertson pupil Behr found 91 per cent with a pupillary width as much as 3 mm., whereas in 64 patients with a partial immobility the corresponding figure was only 6 per cent. He has also been able to establish statistically that the more pronounced the immobility, the narrower, as a rule, the pupil. In no other form of reflex immobility is the myotic tendency so pronounced as in the syphilitic disorders. Simultaneously with the appearance of the myosis, the stroma of the iris is altered. Its radial balks are all elongated, giving the impression of being atrophic. Behr denies the existence of any atrophy and would regard the characteristic appearance of the stroma of the iris in myotic stiffness as merely an effect of the stretching. He argues that if such pupils are dilated the phenomenon will become fainter as the tissue of the iris relaxes in dilatation. Another important symptom worthy of attention in the torpid pupils is, according to Behr, the strong pupillary peristalsis. With the aid of appropriate, delicate

instruments the margin of the pupil in such cases is observed to be in continuous irregular, sluggish vermiculation. This peristaltic unrest gradually disappears, as the immobility becomes more pronounced. In two cases Behr has been able to establish such peristalsis in pupils which were still reacting normally to light. Evidently it can occur as a premonitory symptom to the reflex immobility. This peristalsis as well as the myosis Behr regards as irritative phenomena in the sphincter apparatus.

Another feature of syphilitic reflex immobility is that it affects both eyes; only very rarely does one eye show abolition of the light reflex, while the other reacts normally to both direct and indirect light. The cases of unilateral pupillary stiffness are of great importance to the theoretical explanation of the phenomenon. Among the most important findings bearing upon this point is that of Behr. He was able to show that the reacting eye responds only, or preferably, on illumination of the temporal half of the retina in the eye affected with pupillary immobilization.

Pupils developing reflex stiffness are, as is well known, mostly of unequal width. More especially in the initial stages anisocoria is the rule. Among 34 cases of partial incomplete rigidity Behr found anisocoria in ten-elevenths of the cases, whereas in 26 of those with bilateral total immobilization he found it only in two-thirds of the cases.

It is evident that any attempt to explain the pathophysiology of Argyll-Robertson pupil cannot ignore all these characteristics of the syphilitic stiffness.

Of course, one finds in the literature many attempts to explain the pathogenesis of the reflex immobilization, but a really satisfactory and incontestable explanation of the phenomenon has not yet been advanced. The greatest difficulties in interpreting the symptom probably lie in the fact that we only very imperfectly know the courses of the pupillomotor pathways. These difficulties already begin in the afferent parts. It is still undecided whether special conductive fibers exist for the pupillomotor function in the optic system. Von Hess holds a unitary opinion—that the visual and the pupillomotor receptors in the retina must be identical. This conception is the predominant one in the literature. Von Hess bases his view on the

statements of Groethuysen, who found in extensive pupilloscopic investigations that the discriminative sensibility to visual and pupillomotor stimuli was injured to the same degree in different stages of optic nerve disorders. But there are cases enough, as von Hess himself points out, that show discrepancies between these two functions and that are difficult to reconcile with this assumption. Such cases are recorded by Behr, Abelsdorff, and others. The examinations were made with a technique that eliminates possible sources of error, by exact observation of the intensity, the angle of incidence and the distance of the light employed. In Abelsdorff's case there was an optic atrophy on the left side with reduction of the visual acuteness to one half the normal and a large defect of the visual field without scotoma. With normal accommodation and normal function of all the external ocular muscles, the pupil of the injured eye was practically immobile to light. The author pronounces the opinion that, as the retina was intact, the immobility of the pupil could only be explained by assuming that in the optic nerve there are two sets of fibres qualitatively different, the visual and the pupillary fibres. Such a case as that of Abelsdorff undoubtedly constitutes a strong argument against the unitary conception. From the fact that the optic nerve contains fibres of two different calibres Gudden assumed that the coarser fibres, which are considerably fewer in number than the finer ones, were pupillomotor. Behr, however, rejects this interpretation. He concludes, as the most probable explanation, that both kind of impulses are at first conducted centrally in the same fibres. He escapes from the difficulties by assuming that within the fibrils of the solitary axis-cylinders of the optic nerves there is a functional differentiation. One part of the fibrils of the axis-cylinder serves the visual, another part, and in fact the most resistant, the pupillomotor function. It may be said about this interpretation that it is in many respects rather strange. The pupillomotor impulses are primarily intended for regulation of the tone of the sphincter pupillae. Their part is to adjust the muscle of the sphincter to varying degrees of illumination. Compared with the purely visual, the pupillomotor function must be considered as a very simple one. If the function of the optic nerve is elicited by electromagnetic oscillations, then, according to Behr's hypothesis, it must be conceded that, if the pupillomotor impulses

have adjusted the pupil to a certain degree of brightness, these pupillomotor fibrils within the optic fibres possess a property of excluding themselves from the visual impulses. This is in disagreement with the "all or none" principle of the nerve-fibre as established by Sherrington. It also seems strange that the visual functions, which attain their highest perfection in higher vertebrates, should utilize the same nerve-fibres as the pupillomotor, which are well developed even in the lowest vertebrates who possess only poorly developed visual discrimination.

The whole question of the central conduction of the visual and pupillomotor functions in one or two different systems of fibres is still unsolved. The above-mentioned cases of Behr and Abelsdorff can scarcely be reconciled with the assumption of only one single species of fibres.

Clinical evidence is in favour, at any rate, of the assumption that the pupillomotor and visual pathways follow each other closely throughout the optic nerve, the chiasma, and the optic tract. In each sector of the tract the pupillary pathway seems to lie in the respective sector of the field of vision (Behr). In the posterior part of the diencephalon the pupillomotor diverges from the visual tract. At the level of the lateral geniculate bodies the pupillary path runs in the anterior arm of the quadrigeminal body and then proceeds along the lateral border of the latter to the middle line. How the pupillomotor impulses reach the oculomotor nucleus (the centre of the sphincter pupillae) has not yet been shown with any degree of certainty. Bernheimer supposed that the impulses reach this centre by way of end-splittings of collaterals from the visual neurones in the optic nerve. According to Monakow, there are here interpolated area-connecting neurones.

That the pupillomotor path in the posterior region of the diencephalon really takes this course is shown by the very conclusive experiments of Karplus and Kreidl. They showed that in operations on monkeys and cats when the superficial fibre tract diverges from the optic tract and runs in the anterior arm of the corpus quadrigeminum anterius towards the middle line, there was a total abolition of the reflex of the pupil to light. They were able to draw the conclusion that this was the only pupillary pathway, the pupillomotor impulses

not reaching the centre of the sphincter in any other way. The findings of Karplus and Kreidl undoubtedly have given the most correct information we possess about the course of the pupillary paths.

To the anatomy of the afferent path of the pupillomotor pathways Lenz has recently made an important contribution. He has studied the human brain by means of the Bielchowsky method and has paid special attention to the above-described fibre path which, on the strength of the investigations of Karplus and Kreidl, we are entitled to assume contains the pupillomotor fibres. He describes this small fibre path in the following manner:

> At the level of the central part of the external geniculate body, and not before, a thin pathway of fibres diverges from its medial margin, taking a medio-dorsal course and increasing in size from the afflux of fibres from the most posterior tractus fibres. In this way a rather broad pathway is formed of beautifully arranged parallel fibres, which leave the external geniculate body and run in the direction of the lateral fissure of the corpus quadrigeminum anterius. Some of the fibres end in this body, but another compact bundle continues forwards up to its rostral border at the level of the habenular commissure. When close to the surface this bundle turns into the dorsal part of the posterior commissure, in which it crosses to the other side. Having passed this crossing it runs in the descending part of the posterior commissure ventrally in the direction of the oculomotor nuclei.

About the efferent part of the pupillomotor reflex arc we have somewhat better knowledge than of the afferent. It is considered as fairly certain that the bilaterally formed medial nucleus of Edinger and Westphal, containing small cells and belonging to the complex of the nuclei of the oculomotor nerve, really is the centre of the muscle of the sphincter pupillae. The fibres conducting centrifugal impulses for the innervation of the sphincter pupillae join the trunk of the oculomotor nerve, passing through this to the ganglion ciliare in the orbit. Thence the impulses are conducted further to the bulb in the Nervi ciliares breves (probably as postganglionic parasympathetic fibres).

This short survey may be considered to contain the most important of what clinical evidence as well as physiological experiment tells us about the pathways of the pupillary reflex to light. The intricate disorders of pupillary functions found in different diseases have prompted various authors to supplement our real knowledge with hypothetical considerations, and not a few have made different

schematic constructions of the supposed pathways of the pupillomotor fibres. Any such schema purposes of course to give an explanation of the different clinical motor disturbances of the pupil. Such schemata have been outlined by Bach, Levinsohn, Liepmann, Bumke, Groethuysen, only to mention the most famous. All these have been thoroughly criticized by Behr. They are considered by him as unsatisfactory and not in accord with known clinical symptomatology.

Behr, himself, has given us a schema of the pupillary pathway. Its chief feature is that it assumes a total central second decussation of all the pupillomotor fibres after they have diverged from the lateral geniculate body. In the first place, the fibres from the extramacular regions of the retina cross. Further, Behr assumes that each macula is connected by pupillomotor fibres with the nuclei of the sphincters of both eyes. His schema explains the anisocoria of the hemianopsy observed after tract lesions. The wider pupil is contralateral to the side of the lesion. The bilateral abolition of reflex to light is supposed to be caused by one single focus located at the central crossing of the pupillomotor fibres, in the region immediately anterior to the quadrigeminal bodies. The myosis is conceived of as an irritative phenomenon, due to the irritation exerted by the lesion on the nucleus of the sphincter from its close vicinity to it. Behr writes as follows: "The regular occurrence of a bilateral reflex immobility of the pupils and also its appearance as an isolated symptom make it at least highly probable that it is caused by only one focus."

The unilateral reflex immobility is thought of as being caused by a lesion distal to the central crossing of the pupillomotor pathways, *i.e.* between this and the nucleus of the sphincter. It is postulated by Behr's schema that between these points run all the pupillomotor fibres of the homolateral nasal halves of the retina. According to it, moreover, these fibres have absolutely no connections with the opposite nucleus of the sphincter. If the assumption be correct, then a lesion that cuts the tract at this distance will shut out all pupillomotor impulses from the same nasal retinal halves. Behr has, in fact, been able to show that in unilateral pupillary reflex immobility the pupil of the intact eye is often partially immobilized in as far as it only or preferably reacts on illumination of the temporal half of the totally immobilized eye, not on illumination of the nasal half. This

finding must be considered as one of the most valid corroborations of Behr's scheme.

We know that the bilateral reflex immobilization of the pupils is a symptom almost exclusively occurring in syphilitic diseases. In these it commonly remains as an isolated symptom for years. According to the conception of Behr we must assume a special predilection of the luetic processes for the region of the central crossing of the pupillomotor fibres. Such a predilection has never been recorded from the very extensive histological postmortem examinations of the brain in cases of tabes or syphilitic meningitis.

The histopathological endeavours to reveal the nature of the Argyll-Robertson pupil have simply all failed. The same may be stated of all the attempts that have been made to prove that the cause of the phenomenon was to be looked for in the sphincter-centre within the oculomotor nucleus or in its vicinity in the region around the Sylvian aqueduct.

In spite of the enormous amount of work that has been bestowed upon this problem, nobody has, in fact, succeeded in proving the existence of constant anatomical destructions that are able to explain the mechanism of the pupillar reflex immobility. I need only refer to the very detailed and extensive criticism recently made by Behr. He ends in the following manner: "On the anatomy of the Argyll-Robertson pupil there are so contradictory statements, that it can be maintained that we know almost nothing." The anatomical failure has caused various authors to try to explain this, the most common and most important of all neurological symptoms, in different hypothetical ways. But the majority of these, too, have not been able to stand against criticism (Behr). The most famous is perhaps the theory of Bumke, who assumes that it is caused by a selective degeneration close to the sphincter centre in the oculomotor nucleus of the reflex-collaterals. Bumke thinks the disappearance of these fibres gives such minute alterations of the histological picture that it will never be capable of demonstration by means of our ordinary histological methods. Similar minute reduction of fibres is shown by Spielmeyer in certain cases of tabes around certain medullary cells.

Bumke's theory was in later years taken up in a modified form by Spiegel. Spiegel's starting-point is the vestibular pupil-reflex found

by Wodak. The latter showed that besides the lateral deviations and nystagmus movements of the eyes there occurs, after rotation of the patient, a contraction of the pupil, which is regularly followed by a dilatation so that the pupil becomes more distended than before the experiment. Spiegel recorded that among 16 cases of bilateral Argyll-Robertson pupil the rotation-reaction of the pupil did not occur in 11 cases, appeared bilaterally 3 times and in 2 cases did not appear on one side, but could be traced in the other eye. Two cases of unilateral Argyll-Robertson phenomenon, in which the pupil of the other eye had good reaction to light, showed a loss of the vestibular reaction in the affected eye. The remaining 8 cases can be summed up as follows: In the eye affected with reflex stiffness the vestibular reactions were lost to the same extent as the immobilization of the pupil was pronounced. If the reflex immobilization was absolute, then the vestibular reaction was entirely lost. Spiegel states that the stimulus originating from the vestibular nerve is stronger to the pupillomotor system than the light stimuli to the retina. The vestibular reaction persists longer than the light reaction in atropinized pupils.

From his experiments Spiegel concludes that all theories are invalidated according to which the Argyll-Robertson pupil is caused by a selective degeneration of optic reflex-collaterals to the nucleus of the sphincter. Then the fact that in the vestibular stimulation there is an abolition of the effect on the internal ocular musculature only, whereas the effect on the striated external remains, would mean a selective degeneration not only in the afferent pupillomotor pathways but also in the posterior longitudinal fasciculus, which according to Spiegel is the way by which the vestibular impulses reach the nucleus of the sphincter. He has further shown that after unilateral extirpation of the labyrinth, the remaining intact labyrinth was able to produce vestibular pupillary reflexes in both eyes. With regard to this he finds the assumption absurd that unilateral abolition of the light reflex and the vestibular reflex of the pupil could be produced by a one-sided atrophy of the pupillomotor and vestibulomotor fibres to the pupillary motor centre. It becomes still more absurd, as he could prove, that the pupillomotor fibres reach the sphincter-centre from above, the vestibular from behind. Spiegel evades the difficulties by assuming a lesion or disturbance of the synapses only between the

vestibulomotor and pupillomotor neurons on the one side and the motor cells of the nucleus of the sphincter on the other side. He finds this theory agrees with the fact that we have not yet been able to demonstrate morphological changes within the sphincter-centre. A lesion of the synapses that only concerns the contact surfaces of the neurons will of course never be demonstrated by our anatomical methods.

Jacobsohn Lask finds the existence of such a lesion very improbable. He finds it difficult to conceive that a lesion so insignificant that it cannot be demonstrated by our ordinary methods could afford an explanation of pupillary disturbances that remain for a life-time or during many years.

Behr is also against Spiegel's theory. He points to the occurrence of pupillary immobility in cases of tumours in the region of the anterior quadrigeminal bodies. In these cases there can be no question of any lesion of the synapses. There must be a selective injury to the pupillo-motor fibres on their way from the lateral geniculate to the nucleus of the sphincter.

Some years ago I undertook a study of the comparative anatomy of the diencephalon. As I have said elsewhere, I was able to show that the diencephalon of birds develops according to the same main principles as those governing the diencephalon of the mammals. There was, before I started this study, a general agreement about the thalamic nuclei, namely, that for mammals they showed a considerable conservatism. All mammals had, according to Sachs, the same thalamic nuclei. Now I was able to demonstrate that the diencephalon of the bird is developed in the same way as that of the mammals. The birds have the same thalamic nuclei as the mammals, though there may be differences in so far as the different nuclei have changed in their mutual interrelation within the two classes. Thus the lateral nuclei of the mammalian thalamus is enormously developed compared with the avian, but even the avian diencephalon has a lateral nucleus. It is impossible to speak of a neo- and paleo-thalamus in the sense of Edinger. I think indeed that one ought to be cautious in the conception of neo- and paleo- parts of the cerebrum as a whole. It may be that this conception has been very fertile as a stimulus to anatomical investigation, but I think it has now been superseded. It is

interesting to note that such an experienced observer as Herrick has cancelled all these ideas in his latest paper on the development of the cerebral hemisphere.

In the present paper I shall omit all discussion of the possible theoretical value of my findings. I was struck by the fact that in the diencephalon so many phylogenetically old fibre systems were found at the surface of the brain immediately beneath the pia. I need only direct attention to tracts like the taenia thalami, fornix, taenia semicircularis, and others.

The entire diencephalon might be compared to a funnel, with the pipe in the infundibulum. The evolution of the diencephalon can be expressed most briefly in the following way: In the course of evolution the walls of the funnel increase in thickness, the funnel being filled more and more with phylogenetically new parts. The major part of the funnel contents is derived from thalamic parts. During the whole evolution the funnel is embraced by the chiasm, the two optic tracts, and the lateral geniculate bodies.

The entire evolution of the diencephalon in the vertebrate series is, above all, marked by the enormous expansion of the thalamo-cortical connections. In lower animals the fibre systems that connect the hemisphere with caudal parts of the nervous system are comparatively poorly developed. In these animals (amphibians and reptiles), the hemisphere is connected with the diencephalon by means of a thin stalk—the *Gehirnstiel* of the German authors. During evolution, in mammals the neurons are greatly increased in number, and as a consequence the "stalk", becomes much broader and no longer corresponds to the designation "stalk", since it forms a massive fusion between the hemispheres and the diencephalon. Hence it comes about that the thalamus is situated not behind the hemisphere as in lower animals but is entirely buried within them.

The optic pathways of the diencephalon are greatly influenced by these evolutionary changes. It is true they do not alter their relative position to the brain-stalk. The optic tract runs in all animals caudoventrally to the brain-stalk, but in higher animals it is elongated so that it reaches around the stalk. The lateral geniculate body is situated in all animals immediately behind the stalk. Through the development of the thalamo-cortical connections it is pressed back-

wards. In this way it is displaced to the posterior part of the diencephalon instead of the anterior part, where it lies, for instance, in the frog. In the primates and in man the lateral geniculate body is not only displaced backwards, but is also rotated latero-ventrally almost 90 degrees. This point remained unnoted until recently. For a long time there has been a great difficulty in homologizing the different parts of the lateral geniculate body for *higher and lower vertebrates*. When this dislocation and rotation are taken into account the homologic question can be easily solved.

As a result of the same evolution the trunk of the optic tract is not only elongated, but also twisted. In this way the twisting of the pupillomacular bundle demonstrated by Rönne and others within the optic tract finds a natural explanation.

All the above-described anatomical facts are of the greatest importance to the understanding of the whole diencephalon, as well as of the principles developed in this article respecting the pupillomotor pathways.

One reason that the development of the diencephalon was not understood until recently was due to the theory advanced by His. He thought that he had proved that at an early embryonic stage there was a fusion of the medial wall of the hemisphere with the lateral wall of the diencephalon. The massive fusion of the optic thalamus with the hemisphere he conceived of as the effect of a growing together of these brain parts. Hochstetter, Goldstein, and others, have shown in ontogenetic studies of the human brain that the idea promulgated by His was wrong. I have been able to demonstrate in my comparative studies how impossible is any assumption of a fusion here. Then, too, if such a fusion really occurred it would mean that the lateral geniculate body and the optic tracts as well would be buried within the brain. The facts are just the opposite; there is no such fusion. The massive connection of the hemisphere with the thalamus is capable of a natural explanation in the way described above. I have dwelt upon these points so long in this discussion because of their importance to our understanding of the anatomy of the optic and pupillary pathways of the diencephalon. Here stress need only be laid upon the fact that the optic pathways during the whole evolution remain on the surface of the diencephalon. The behaviour of the

optic pathways forms a strong argument in favour of the general principle that the phylogenetically old systems are generally to be found on the surface of the brain.

This is also a ruling principle within the optic system of the diencephalon itself. An investigation of the course of the different fibre groups within the optic nerve, the chiasma, the optic tract, and the lateral geniculate body will show that all the phylogenetically old fibre systems run on the surface.

The macular fibers are the most important recent acquisition of the higher mammals. We know from a long series of reliable investigations that the macular tract always runs in the centre of the chiasm, the optic tract, and in the inferior parts of the lateral geniculate body. This has been shown very beautifully in the thorough investigation of Brouwer and Zeeman. These authors have found that the fibres from the phylogenetically older parts of the retina, *i.e.* the field of monocular vision (the nasal margin of the retina or the temporal sector of the visual field), run in a marginal sheath of the optic tract. These fibres continue to the ventral layer of the large cells of the lateral geniculate body. We know from many signs that this layer is, phylogenetically, the oldest part of the geniculate body. For instance, according to Kappers, these larger cells persist after ablation of the cerebral cortex, whereas the central regions all atrophy. I would direct attention to the fact that this layer is situated immediately beneath the surface of the brain substance. It forms the most superficial layer of the geniculate body.

I would also draw attention to another fact. When using the impregnation method (the silver-pyridine method of Ranson) there are unmyelinated fibres to be detected in the optic nerve, the chiasm, and the optic tract. I have investigated this in the rabbit, cat, monkey, and man. Constantly to be found are these unmyelinated fibres. And they are collected in the surface layer of the chiasm and the optic tract, at least in its rostral parts. In the posterior regions of the optic tract I have not been able to detect such naked fibres. This may, however, be due to poor preparations, for we know that these impregnation methods are all very capricious in their working. In the chiasm the occurrence of unmyelinated fibres can be constantly demonstrated on the surface. In the optic nerve they can be followed

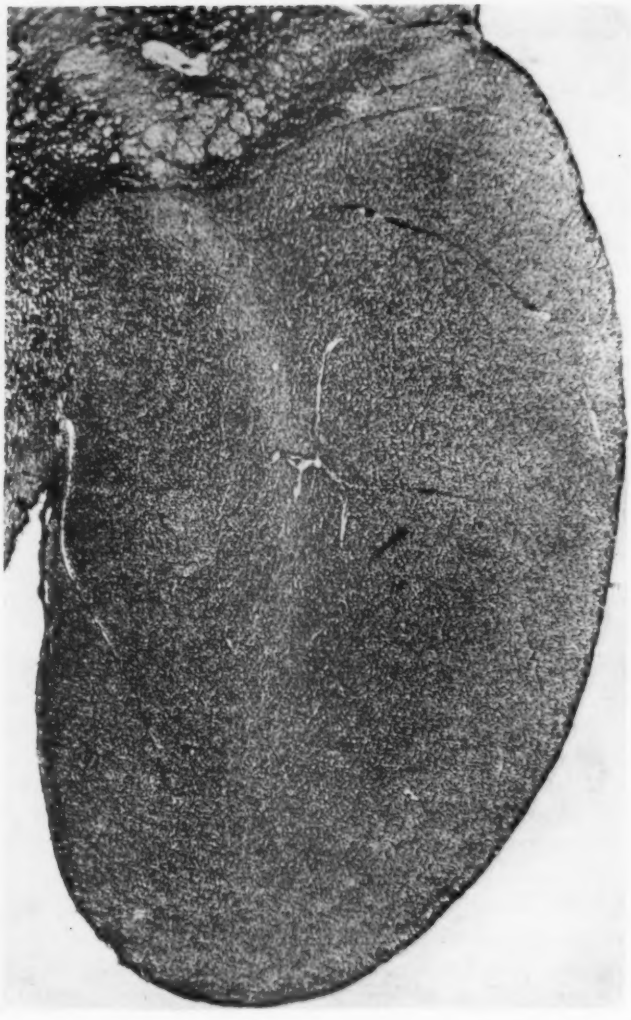

FIG. 1. NORMAL OPTIC TRACT. (PYRIDINE-SILVER ACCORDING TO RANSON.) ×45

more particularly on the medial surface. By and by they lose themselves in the interior of the optic nerve and its different fascicles, and here are found in the surface layers of the fascicles immediately beneath the intraneural septa.

Without doubt these unmyelinated fibres belong to the phylogenetically old fibre systems of the optic pathways.

We know that the nervous system of lower animals is richer in naked fibres than that of higher animals. The higher the development proceeds, the greater the relative increase in the number of the unmyelinated fibres. In an earlier work I have directed attention to this fact, first demonstrated by Ranson for the posterior spinal roots. At the entrance to the spinal cord these roots are coated with a thin sheath of unmyelinated fibres, whereas the myelinated fibres run in the centre of the root. Undoubtedly, we are entitled to interpret the arrangement of different layers within the roots as an expression of phylogenetic principles. The unmyelinated superficial fibres are the older ones. As is well known, Ranson has for years favoured the theory that the unmyelinated fibres within the posterior roots conducted the phylogenetically old protopathic sensibility. Thus, in the optic system also, we have the right to conclude that the fine fibres on the surface represent the phylogenetically older functions.

From all these considerations the idea follows that the pupillomotor pathways within the optic system are to be looked for on the surface of these formations, the optic nerve in its most caudal parts, in the chiasm, and in the optic tract. The examples given may suffice to show that the optic system of the diencephalon is constructed according to the law that the phylogenetically more recent systems are to be found inside in the central regions of the transverse sections, whereas the phylogenetically older parts lie on the surface.

Of the pupillomotor path we know with certainty that it really takes a very superficial course for a long distance. At the level of the lateral geniculate body in its rostral region it diverges and runs dorso-medially towards the middle line anterior to the anterior quadrigeminal bodies. This tract contains strongly myelinated fibres but also a considerable number of unmyelinated fibres in ape and man; in the two latter I have been able to investigate this point by means of silver impregnation methods. Brouwer and Zeeman

conclude from their experiments that if there really are pupillomotor fibres from the macula to the quadrigeminal body, they must be unmyelinated. It is not improbable that the fibres detaching themselves from the optic tract in this region in order to run on the surface must for a certain distance have belonged to the most superficial fibres of the optic tract itself. Thus, we really do have a good deal of exact knowledge about the surface route of the pupillomotor tract. According to my theoretical deductions these pathways are to be expected to run also on the surface of the chiasm and of the posterior part of the optic nerve.

The superficial course of the pupillary pathways must be of the greatest importance for our understanding of the pathogenesis of the pupillary disturbances in meningitic processes involving the surface layers of the diencephalon. In no other region of the central nervous system does the tabetic process appear as a surface alteration as it does in the basal regions of the brain. Since Elschnig proved that the degeneration of the optic nerve and the optic tract was not caused by meningitic or vascular processes but was due to purely parenchymatous changes, a succession of authors have occupied themselves with the pathogenesis of optic atrophy (von Gross, Stargardt, Igersheimer, Richter, and Behr). They all agree that the degeneration always begins in the marginal regions of the optic system. As to the starting-point there is no agreement. Stargardt finds the atrophy to commence within the chiasma. This is denied by Igersheimer and Behr, who found its beginning within the optic nerve. Igersheimer thinks that the commencement of the process is in the most distal or retrobulbar part of the optic nerve. Behr expresses this precisely in the following way. He finds that the atrophy may start at any point of the optic nerve. The posterior limit for this degeneration is the level of the glia list in the optic nerve, immediately rostral to the chiasm, where the optic nerve loses its septal system. The optic pathways are injured only where the nervous tissue by way of the extended septal reticulum and the pia comes into close contact with the connective tissue. The connective tissue, according to this author, is the nesting place of the spirochetes and their toxins. The primary feature of the atrophic processes is the injury not only to the marginal glia but also to the parenchymatous glia fibres. On this

FIG. 2. OPTIC TRACT IN A CASE OF TABES SHOWING THE CONCENTRIC MARGINAL DEGENERATION. (PYRIDINE-SILVER ACCORDING TO RANSON.) × 60

follows a disturbance of nutrition of the nerve fibres, and they disintegrate. The syphilitic toxins produce at first changes in the septa of the optic nerve, and these result in a disorder and functional disturbance of the glia fibres, thereby interfering with the nutrition of the nerve fibres so that they atrophy.

In the medical clinic in Lund I have examined sections from a very early case of tabes. This patient had died from heart disease. Among the clinical symptoms of the case reference may be made to a bilateral Argyll-Robertson pupil and impairment of the patellar reflexes on

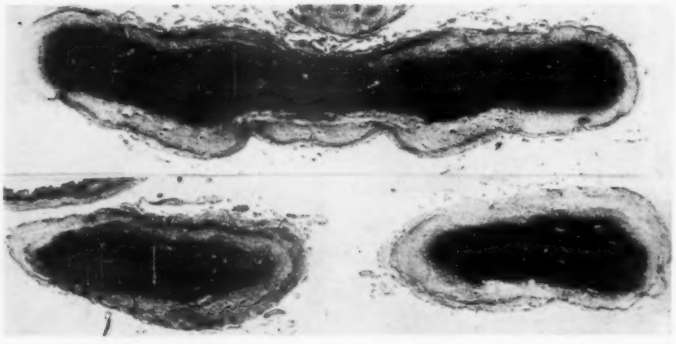

FIG. 3. OPTIC CHIASMA AND NERVES IN A CASE OF TABES SHOWING THE CONCENTRIC MARGINAL DEGENERATION. (PYRIDINE-SILVER ACCORDING TO RANSON.) ×40

both sides. The Wassermann reaction was positive. The patient died only a few days after admission, a thorough clinical examination thus being made impossible. There was therefore no examination of the visual fields.

The brain-stem was prepared in order to study the pupillomotor pathways. It was cut in slices, which were impregnated with silver according to the Cajal-Ranson method. A continuous microscopic series was cut. The preparations show very clearly a marginal degeneration that begins in the optic nerve, is very marked within the chiasma, and continues through the optic tract. Especially in

the anterior part of the last mentioned is the marginal degeneration zone very distinct. The parenchyma is here rarified in a most distinct manner owing to the disappearance of fibres. A particularly striking feature is the concentric character of the degenerative zone. The internal border of this zone is absolutely parallel to the external surface.

In addition, there was a widely extended meningitic infiltration in the basal subarachnoidal spaces. The pia was increased in thickness by inflammatory infiltrations. Thus, on the base of the brain in the intrapeduncular spaces, in the region around the third ventricle and the quadrigeminal bodies, there were very marked meningitic alterations. Corresponding to these meningitic changes were widely extended marginal degeneration zones.

I paid special attention to the superficial fibre tracts leaving the optic tract and running in the anterior arm of the anterior quadrigeminal body. Also in this case they were involved in these marginal degenerative zones.

As to the cause of these marginal degenerations there is no agreement. For the most part meningeal infiltrations are rejected as causes, as they often occur without producing degeneration (Spielmeyer). A marginal zone of this nature with an internal border line running exactly parallel to the external surface cannot of course have a vascular cause. It might be thought to be produced by a superficial stasis of the lymph resulting from the pial infiltration. Whatever the genesis of this typical degenerative zone may be, one thing is certain, it can only be produced by an agent primarily acting on the nervous system from the subarachnoidal spaces.

The pictures given in this case agree perfectly with the statements of earlier authors. They should be of great assistance for our understanding of the nature of the tabetic process as a whole.

These degenerative marginal zones supply an illustration of the tendency within the literature of later years to conceive of the tabetic process as one that attacks the central nervous system in some not yet clearly defined way, from the subarachnoidal space. Thus Hauptmann considers the tabetic processes to be the effect of syphilitic toxins circulating in the fluid within the subarachnoidal spaces and from these spaces attacking the neuraxis. Just as Spielmeyer after

endolumbal injection of stovaine in dogs found a typical marginal degeneration, so Hauptmann found, after endolumbal injection of normal serum, a similar degeneration which he considered as recalling the tabetic. Recently Spitzer, of the Marburg Institute in Vienna, published an article in which he defends the conclusion that the tabetic process is produced by syphilitic toxins in the subarachnoidal spaces. He emphasizes that all anatomical changes in this disease are to be found where the neuraxis is bathed in the cerebrospinal fluid.

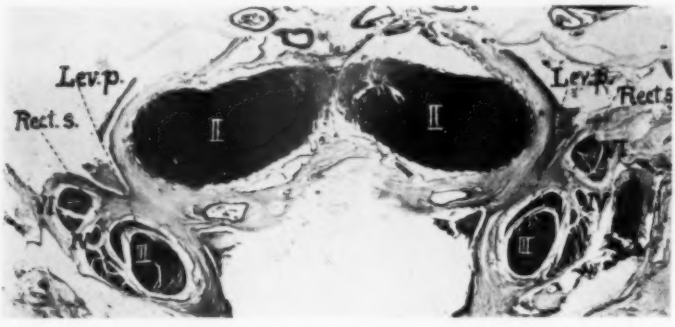

FIG. 4. TRANSVERSE SECTION THROUGH THE ANTERIOR REGION OF THE CHIASMA IN MACACUS WITH NERVES OF THE EYEMUSCLES IN SITU. (PYRIDINE-SILVER IMPREGNATION ACCORDING TO RANSON.)

Note how the upper branch of the oculomotor nerve, which contains the fibres to the M. levator palpebrae and the M. rectus superior, forms in the section a moon-shaped figure, that rides on the main stem of the third nerve.

He states that metalues is a bacterial infection of the subarachnoidal space. A similar idea was developed as early as 1909 by Heym.

In no other region is the proneness for marginal degenerations so strong as in the basal regions of the brain. The same holds good for the oculomotor nerve. Concerning metaluetic palsy of the oculomotor nerve a long line of authors (Stargardt, Igersheimer, Richter, Spitzer, and others) have established, in a large number of cases, that there are diffuse perineuritic infiltrations in the oculomotor nerve trunk that cause marginal degenerations in it. I have directed attention to the fact that these infiltrations must in the first place attack the fibres

running on the surface of the nerve trunk. In a previous article I have maintained that the fibres of the levator palpebrae form the most superficial sheath of the nerve fibres. The clinical experience that oculomotor palsy in tabes begins with a ptosis is in this way capable of a natural explanation. During the last year I have examined the course of the fibres running to the M. levator palpebrae and the M. rectus superior in apes. At first I tried to investigate it in man, but owing to the length of the nerve in the human, it offered

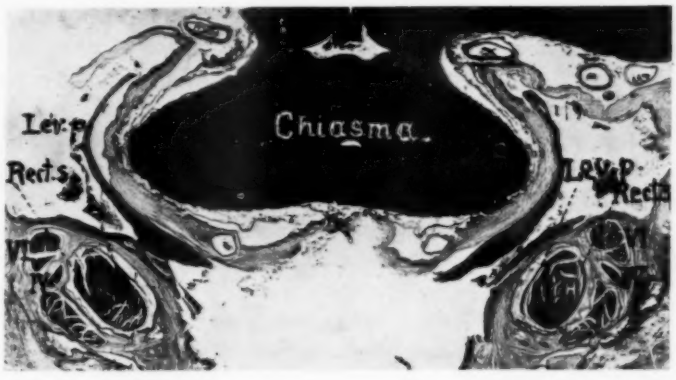

FIG. 5. TRANSVERSE SECTION THROUGH CHIASMA OF MACACUS; FROM THE SAME SAME SERIES AS FIGURE 4

The fibres to the M. levator palpebrae are forming a superficial sheet of the medial side of the main stem, whereas the fibres to the M. rectus superior are running on the lateral side. Around the nerve-stem the subarachnoidal space is seen with typical balks. (Section at the level of the cavernous sinus.)

considerable difficulties. In a macacus, when the optic bulb and the whole content of the orbit was left in position with the brain-stem, it could very definitely be shown in a complete microscopical series (Ranson method) that in the anterior portion of the oculomotor nerve, at the level of the entrance through the dura, the superior branch of the oculomotor nerve containing the fibres to the M. levator palpebrae and the M. rectus superior formed on the transverse section a lunule, riding dorsally on the inferior branch, the main stem. Following the

stem backwards it can very definitely be demonstrated that the branches of the lunular figure are elongated ventrally, so that they finally embrace almost the whole circumference of the main stem. In this way the levator fibres and the fibres to the rectus superior muscle really form a superficial sheath of the nerve within the subarachnoidal space. As there is no rearrangement of the fibres further back, it is to be supposed that the fibres of these muscles preserve their superficial location in the transverse section throughout the whole course of the nerve. This explains why ptosis is such a common symptom in luetic diseases of the brain. It explains why it so often is an isolated or a premonitory symptom. It is evident that luetic meningitis must in the first place attack the surface fibres. In this way a natural explanation is furnished for the old clinical statement that in lesions of the oculomotor nerve trunk the upper lid is first dropped, after which behind the "dropped curtain" the palsy analysis becomes complete.

It is also an old clinical experience that in the lesions of the nucleus of the oculomotor nerve the opposite is the case. Here the levator is preserved until the final stage. The course of the fibres from the levator at the circumference of the nerve stem justifies the conclusion that the levator fibres must be represented in the majority of the nerve filaments entering the brain. This means that the levator fibres must be represented throughout a long distance within the oculomotor nuclei. In this way it is possible to account for the fact that in nuclear lesions the levator functions are spared to the very end, or appear very late in the course of the paralysis.

We have already given the evolutionary reasons for expecting the pupillomotor pathways to be found on the surface of the diencephalon as one of the phylogenetically oldest pathways of the optic system. We know that these pathways really take a very superficial course on the way from the lateral geniculate body to the anterior quadrigeminal body. As a complete series of microscopic sections shows that there is no rearrangement in the tractus opticus, it follows that these fibres must for a long distance belong to the surface fibres within the optic tract. Moreover, since we have absolute knowledge that the luetic disorders of the brain proceed with extensive meningeal, subpial infiltrations along the pupillomotor pathways, it appears an imperative

logical necessity to consider the common pupillary disturbances in these disorders as due to the meningitic infiltrations and the marginal degenerations within the basal regions of the brain.

From this point of view the reflex inhibition of the pupillary reaction to light can, in my opinion, be explained together with all its clinical characteristics.

The surface route of the pupillary pathways explains why the Argyll-Robertson pupil is a symptom almost exclusively occurring in luetic and especially metaluetic disorders. And besides, no other diseases produce such gradually developing marginal destruction in the surface layers of the central nervous system as the luetic. We understand how tabes and general paresis have acquired their monopoly in producing the Argyll-Robertson pupil.

The question must be raised how far other meningitic processes are able to produce reflex immobility in the same way. In septic and tuberculous meningitis the basal regions and subarachnoidal spaces are all implicated in meningitic processes. There are more or less pronounced inflammatory changes of the meninges. Indeed, the general experience (Spielmeyer) is that the meningitic infiltration as such does not give the marginal degenerations, even in tabes. There is a general agreement that to produce the degeneration another factor is necessary besides the infiltration. This may explain why in ordinary forms of meningitis (tuberculous, encephalomeningitic, and others) the immobilization of the pupil only occurs as a rare phenomenon. The general progress of these diseases is also much more rapid. That means the rapid sequence of all kind of complications. In this way we do not get the opportunities to study the pupillary symptoms in so pure a form as in slowly progressing meningitic processes (luetic).

So slow and benignant a process as the luetic would naturally attack the surface fibres long before those lying deeper. This explains why the pupillary stiffness sets in long before other manifestations of the disease. It explains why the stiffness can persist as an isolated symptom for years. It is in this way also possible to account for the fact that an isolated Argyll-Robertson pupil exists without any other disturbances of optic functions, above all without impairment of the visual fields. In tabes these impairments vary in their nature. But

there is a general agreement that the common type of impairment of visual fields in tabes is the concentric reduction. This is in complete concordance with the thesis of this article. The peripheries of the visual fields are represented in the surface layers of the chiasma, the tractus, the lateral geniculate body, and so forth. Naturally the marginal degenerative processes must in the first place attack these fibres. The peripheries of the visual field represent the phylogenetically oldest part of the visual functions.

This conception enables us to understand why the pupillary disturbances are generally bilateral, and the meningitic and tabetic processes are mostly bilateral. Hence it follows that both eyes are involved in the processes.

The unilateral Argyll-Robertson pupil is a great clinical rarity. We assume with Behr and others that it is caused by a focus behind the central crossing of the pupillomotor fibres. This crossing probably occurs in the dorsal, the most superficial parts of the posterior commissure immediately rostral to the anterior quadrigeminal bodies. Lenz, who gives the most detailed description of this pathway, emphasizes that it runs immediately beneath the surface. In view of the great power of variation generally shown by luetic disorders, it cannot be considered extraordinary that in rare cases the lesion is limited to exactly this region.

As the surface course of the pupillomotor pathways is well established for the stretch from the lateral geniculate body to the posterior commissure, and is probable within the chiasma and the optic tract, we may conclude that the degenerative zones must involve the pupillomotor pathways wherever they are situated in the basal subarachnoidal spaces. As we know, the luetic changes show a definite predilection for these basal spaces. In this way we dispense with any supposition of one single focus producing the bilateral Argyll-Robertson pupil. As you know, most of the different theories advanced to explain the Argyll-Robertson pupil have had to take into consideration its most common features, also its bilaterality. A single focus has then generally been assumed, and in later investigations this focus has been assigned to the region of the quadrigeminal bodies. Here we must bear in mind that despite the very extensive anatomical investigations we have never been able to establish a focus in this

region. If one realizes the enormous amount of work that has been devoted to the anatomical study of the Argyll-Robertson pupil, it must be considered very strange that, if such a focus really does exist, it should constantly escape the attention of all these minute investigations and remain unrevealed. With the conception of the surface course we need not resort to any hypothetical foci. We are able to connect the pupillary disturbances with the actually existing anatomical lesions, the meningitic changes, and the marginal degenerations of the optic pathways so well known to all who have made a study of syphilitic brain diseases.

It is natural that the tabetic process with its pial infiltrations and inflammatory changes and its degenerations must exert an irritation on the pathways in its way. In the spinal cord the paraesthesias, the lightning pains, and the tabetic crises are all considered as irritation phenomena emanating from the posterior spinal roots. Similarly, we must assume that the cerebral pathways engaged in the processes are in a condition of irritation. Like Behr, we are inclined to regard myosis, and especially the above-described peristalsis of the pupillary margin in the initial stages, as signs of irritation of the pupillomotor fibres in their course through the subarachnoidal spaces to the centre of the sphincter muscle. We are liable to get these irritation phenomena of the meningitic processes wherever they may be located within the basal cerebral spaces. We can also, as regards the irritation phenomena, dispense with the assumption of a single focus which has never been found.

From this viewpoint the pupillary disturbances and the lightning pains, the crises and so on, are equivalent phenomena. In fact there is in the literature at least one case published (Cassans, Chiray and Mantoux) in which the Argyll-Robertson pupil existed intermittently only during the gastric crises. Such cases, if observed further, will greatly assist in the theoretical understanding of the tabetic process as a whole.

Myosis, by several authors (Redlich, Spiegel), is referred to the abolition of the sensory and emotional dilatation of the pupil. Spiegel has applied his line of thought also to the sensory pupillary reflex. Together with Gozzano he has shown for cats, in which the cervical sympathicus had been bilaterally cut and in which thus the pupillary

dilatation could only represent an inhibition of the tonus of the third nerve, that a destruction of the roof of the aqueduct and the central gray matter of the anterior quadrigeminal body did not abolish the pupillary reaction to pain. This inhibition of the sphincter centre produced by painful stimuli must thus reach the sphincter nucleus ventrally. Spiegel considers this as still another proof of his view that in the presence of the Argyll-Robertson pupil the lesion can only be in the synapse between the cells of the sphincter and the afferent neurones.

Redlich also interprets myosis as a result of the abolition of the sensory pain impulses, due to the degeneration of the sensory neurones in the posterior columns of the spinal cord. But Behr is not in favour of this view because the myotic Argyll-Robertson pupils appear a long time before there are any sensory disturbances, and their progress is not accompanied by an increase in the intensity of the myosis. With the explanation given above of the genesis of the pupillary disturbances, myosis is naturally considered as due to a contraction of the sphincter muscle produced by irritation from the meningitic processes. In this tonically contracted muscle the sensory impulses for dilatation cannot act. We need not consider the abolition of pupillary reaction to pain as a sign of any lesion of any definite fibre-paths. In the tonically contracted pupil the pain reaction is simply lost. In this way we are inclined to explain the abolition of the vestibular reaction in reflex immobilized pupils as demonstrated by Spiegel.

Schaffer has especially emphasized that the degeneration of fibres within the posterior spinal roots in tabes is not a diffuse one, but that the fibres gradually disintegrate one by one. This is confirmed by Richter. The pictures of degeneration within the spinal cord are to be considered as summations of such degenerations of single fibres, especially in the early stages of tabes. So undoubtedly is also the process in tabetic degeneration of the pupillomotor fibres of the diencephalon. This explains why the Argyll-Robertson pupil develops slowly and in successive steps. There is at first only a slowness and retardation in response to light, which gradually turns into complete loss of reaction. The disintegration of single fibres explains why the process in the initial stages does not attack the pupil symmetrically. Different sectors are differently attacked. In this way we understand the

asymmetry of the pupils in the initial stages. We understand further why this asymmetry appears only in the initial stages. As the disintegrating process goes on, the entire mass of pupillomotor fibres will become involved. In like measure the reflex stiffness develops and becomes absolute. The pupils are implicated in the process along the whole periphery. At that stage the pupillary peristalsis is lost and the myosis is also complete. Perhaps in the final stages the constricting impulses in accommodation play a rôle in the final total myosis, as Spiegel thinks.

Besides myosis, anisocoria is one of the main features of the clinical picture of Argyll-Robertson pupils in lues. This is naturally to be explained as the effect of an asymmetric lesion of the pupillomotor pathways. A tendency to anisocoria already exists from the fact that each optic tract influences each sphincter centre with a different pupillomotor force. From the anisocoria produced by a lesion of a tractus (paralysis), it must of course be concluded that an irritation of a tractus must also give an anisocoria, but of an opposite character to that after tractus paralysis (myotic pupil on the same side as the lesion). The anisocoria in metalues must, if this is right, be a feature of the initial stages. We know that such is the case. As the metaluetic process goes on, as the meningitic processes within the basal subarachnoidal spaces progress, in the same degree is the chance increased of all the fibres of the pupillomotor pathways being affected somewhere or other. In this manner the process will become symmetric, even as regards the eyes. Thus, in the advanced stages the anisocoria will not occur with the same frequency.

If the assumption of the superficial course of the pupillomotor fibres (even in the chiasma itself) proves to be correct, then the tabetic process need not be symmetrical within the basal subarachnoidal spaces in order to give symmetric contraction of the pupils. If the entire pupillomotor pathway is attacked on both sides somewhere on its surface course, the effect will be a symmetric contraction, an isocoria. Even in this respect we do not need the assumption of one single focus causing the bilateral Argyll-Robertson pupil.

The above-mentioned mode of considering the genesis of the Argyll-Robertson pupil enables us to understand why in some cases it disappears after treatment. In such cases we may be entitled to assume

that it is caused by meningitic infiltrations that are dispersed by the antiluetic treatment. We understand also why it can persist as an isolated symptom for years after the luetic processes have come to a standstill. We are not astonished to find in the literature that the anatomical investigations have not been able to reveal the changes causing the Argyll-Robertson pupil in cases where the luetic process had been clinically healed for many years (Nonne, Marburg). If the brain is not treated by special histological methods and if special attention is not directed to these surface layers of the optic pathways, the loss of fibres will certainly easily escape the attention.

It is clear that the more the luetic process proceeds, the more formations other than the pupillomotor and the visual pathways will be attacked. In this way all kinds of clinical complications may arise. In like manner the development of the reflex immobility of the pupil to absolute immobility will be explained. Undoubtedly, changes in the oculomotor nerve trunk greatly contribute to this.

Our mode of reasoning helps us to understand why the pupillary disturbances are so typical of syphilitic brain diseases. Except the syphilitic no other diseases give slowly developing marginal lesions of the basal regions of the brain. Only a disease that produces such lesions will be able to produce the Argyll-Robertson phenomenon.

In later years records have been accumulating of cases of abolition of the pupillary reaction to light after severe traumatism of the skull. Especially during the war a great number of such observations were made (Guillain has published a long series). Nobody has been able to give a reasonable explanation for these cases. In the majority the traumatism was a very severe one. It is a rule that almost all the patients showed signs of a cerebral commotion. We know that such a commotion means a grave lesion to the brain and that the cases are very often, if not always, marked by hemorrhage of the meningeal spaces. With the above conception it must be considered quite natural that extended bleeding in the basal subarachnoidal spaces, with resting coagula, and traumatic arachnoiditis will exercise an influence upon the superficial oculomotor fibres. If, for instance, the optic tracts and the chiasma are embedded in blood clots, the pupillomotor pathways will also, it is reasonable to think, be affected. I should be inclined to explain the traumatic pupillary disturbances

on this basis. Guillain has found in a certain number a yellowish cerebrospinal fluid on lumbar puncture. He emphasizes that this was by no means noted in all of his cases. On the other hand, it may be assumed that all hemorrhages of the basal subarachnoidal spaces of the brain will not give traces of blood on lumbar puncture.

This explanation of the traumatic pupillary disturbances seems to me more natural than the assumption of a lesion of the brain substance within the region of the quadrigeminal bodies. Of course, a lesion there certainly could occur as well as in other parts of the brain in severe traumatisms. But on the side we know that the lesions in such cases are especially located as contrecoup phenomena in the parts near the bones of the cranial cavity. Thus, for traumatism, the region of the quadrigeminal bodies belongs to the less exposed parts of the brain.

In the literature there is clear evidence that the general type of pupillary disturbances caused by traumatism is not the Argyll-Robertson pupil, but the so-called amaurotic stiffness. This kind of immobility, unlike the Argyll-Robertson pupil, is characterized by the complete loss of any reaction in the involved eye combined with loss of consensual reaction in the other eye. Cases of this nature are described after orbital traumatism as showing slight impairment of the visual function in the involved eye. Such cases according to my ideas could be explained as caused by bleeding into the perineural sheath of the optic nerve. In fact there is one such case published (Marx, 1908) in which the immobilization of the pupil to light was caused by a hematoma of the perineurium of the optic nerve. As the majority of cases with this lesion are cases of orbital traumatism, they will certainly also very often be complicated with such hemorrhages into the sheaths of the optic nerve. They can hardly be conceived of as not being complicated by such bleedings. Groethuysen found that in acute retrobulbar neuritis the pupillomotor and the visual power of discrimination are reduced in the same degree, whereas the chronic forms are characterized by a more marked impairment of the pupillomotor reaction. This also is in complete accordance with the above ideas. In acute neuritis there is a diffuse involvement of the whole parenchyma of the optic nerve, oedema, hyperaemia, and so on. But in the chronic forms there is hypertrophy of the connective tissue, the

perineurium, and the septa. Such a chronic change of the perineurium is liable to give pupillomotor disturbances earlier than the visual ones. The superficial course of the pupillomotor fibres can also be used to explain the forms of pupillomotor disturbances after traumatism and neuritis.

With this explanation of the genesis of the pupillary disturbances in lues, traumatism, and other conditions we are able to understand why other severe organic brain diseases so rarely give the Argyll-Robertson pupil. We understand why in disseminated sclerosis this symptom is such an extreme rarity. This disease can only bring about reflex immobilization of the pupils if a focus is situated exactly in the spot where Behr supposes the luetic or metaluetic lesion is situated. This spot is immediately rostral to the anterior quadrigeminal bodies. Or the same result will be produced if the lesions are located symmetrically in the two optic tracts. But we know that the most important feature of this disease is that the myelin sheaths degenerate first of all, whereas the axis-cylinders exhibit a greater resistance to pathological destruction. This may also be one of the reasons why the pupillomotor functions are spared and that the Argyll-Robertson pupil is such a rarity in this disease.

In epidemic encephalitis, pupillary disturbances must be expected. Indeed, they are very common. We explain them as caused by lesions of the oculomotor nucleus. The genuine Argyll-Robertson pupil is an extreme rarity. In epidemic encephalitis, which is characterized by meningitic changes, the Argyll-Robertson pupil would, according to our above-mentioned deductions, be a common symptom. How is this paradox to be explained? The general type of encephalitis is much less destructive than, for instance, that of poliomyelitis. It does not give the above-described marginal degenerations within the brain-stem, so common in lues. And only a lesion characterized by destruction of the surface layers in these regions is liable to give the Argyll-Robertson pupil. Thus the rarity of the Argyll-Robertson pupil in encephalitis epidemica is in complete accordance with what has been said above.

CONCLUSIONS

For the evolutionary reasons developed in the foregoing pages we have to look for the pupillomotor pathways on the surface of the

diencephalon. We know for certain that they take a surface route from the posterior part of the optic tract to the anterior commissure in front of the anterior quadrigeminal bodies. As the metaluetic and luetic meningitic processes produce successively developing marginal degenerations of the optic pathways as also of the diencephalic parts on the whole, the pupillomotor pathways must be injured at an early stage. In fact all the characteristic features of the Argyll-Robertson pupil are to be explained in this manner. The reflex immobility of the pupil is to be considered simply as a meningitic symptom. In this way only does the Argyll-Robertson pupil acquire significance clinically. The disturbed pupillary reaction to light reflects the processes within the basal subarachnoidal spaces along the optic pathways. It appears to be a very sensitive indicator of these processes when the disturbance occurs in the very early stages. Such an indicator is certainly also the isolated ptosis in metaluetic processes. In the same way we attain to an understanding of the pupillary disturbances after traumatic lesions. As all the evidence indicates that only such morbid processes as manifest themselves in producing marginal destructions within the basal subarachnoidal spaces of the brain are able to cause the Argyll-Robertson pupil, we understand that the metaluetic and luetic diseases hold a monopoly among the causes of this valuable clinical symptom.

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THE JOHNS HOPKINS MEDICAL RESEARCH CLUB

CLINICAL ASPECTS OF SICKLE CELL ANEMIA[1]

HUGH JOSEPHS

From the Department of Pediatrics

The clinical findings in twelve cases of active sickle cell anemia were briefly summarized, together with the experiences in looking for latent cases among the colored children admitted to the hospital. The separation of "active" from "latent" cases was made on the basis of increase in hemolysis alone. The salient points were the following:

1. Of 250 colored children taken at random, 16 showed the characteristic changes in the blood. Of these 16, none were anemic, and the fact that they had the latent condition was in no case suspected. Nine of these cases occurred among 44 cases of pneumonia, but no conclusions could be drawn from this fact. There was no relation between the latent condition and any disease other than pneumonia. The mortality among these children and their families was not demonstrably higher than the average. In one case with pneumonia, there developed jaundice together with a rapidly falling hemoglobin, otherwise the sickness from which the child suffered did not influence the latent sickle cell condition in any way.

2. Symptomatology of active cases: Similar in all respects to those reported in the literature. Emphasis was placed on the incidence of joint symptoms similar to those of rheumatic fever. Nervous symptoms occurred, but not with sufficient regularity to make clear any relation between them and the sickle cell anemia. The tendency was for the hemoglobin to remain at a definite level which varied with the individual, and lay somewhere between 35 and 60 per cent. The effect of transfusion was only temporary during the quiescent stage, and the hemoglobin tended quickly to return to its characteristic level. Exacerbations when they occurred were short in duration, but might be severe enough to cause death. If the patient survived,

[1] Presented October 26, 1928.

the hemoglobin tended to rise slowly to its characteristic level. Transfusion given during an exacerbation was effective in hastening this return. A study of urobilin excretion in one case with markedly increased excretion showed the effect of transfusion in decreasing, and the effect of infection in increasing its rate.

3. The liver was regularly enlarged, and in one case cirrhosis was present. The presence of cirrhosis, however, was thought to be a coincidence, as there were no characteristic lesions found in the liver in the other cases coming to autopsy.

4. The spleen varied, tending to increase in size during the periods of exacerbation, in one case very markedly so.

5. The findings in the heart were of interest since they gave rise to the diagnosis of endocarditis in several cases. The cardiac manifestations will be the subject of a paper soon to be prepared.

6. In one case there was arterial hypertension with a tendency to fixation of specific gravity of the urine, both of which cleared up promptly following transfusion.

7. In one case there was a development of the active phase from the latent phase during an infection and a later return to the latent condition. This is the only case in which there was a tendency to return to the latent condition once the active condition was established.

8. Of the twelve cases, five died. Dr. Rich will discuss the autopsies. Two cases have been followed for five years, both continue to have hemoglobin values of about 50 per cent, but show no disability therefrom.

THE SPLENIC LESION IN SICKLE CELL ANEMIA[1]

ARNOLD RICE RICH

From the Department of Pathology

A study of the pathological histology of five clinically diagnosed cases of sickle cell anemia disclosed such a striking and unusual lesion in the spleen that it was believed possible to be able to recognize this malady by the histological study of the spleen. Accordingly, a certain number of spleens from recent routine autopsies were examined, and

[1] Presented October 26, 1928.

four cases were found in which the sickle cell condition had not been suspected clinically, but in which the spleen showed the lesion which had been found in the clinically diagnosed cases. The names of these autopsied individuals were given to Dr. Josephs who examined the blood of members of their families, and in each case he found the sickle cell trait in an immediate relative, in conformation with the hereditary nature of the condition.

The sections from five thousand consecutive autopsies, performed in this department during the last ten years, were then studied microscopically, and in sixty-two cases the splenic lesion which had been found to be characteristic of sickle cell anemia was discovered. None of these cases had been recognized, either clinically or pathologically, as sickle cell anaemia. All were negroes. Sickle cells were found in the blood in the histological sections in every case.

The peculiar splenic lesion characteristic of this condition, and present in latent as well as in active cases, consists in a congenital malformation of the sinuses of the spleen, which permits the free escape of blood into the pulp. The entire pulp may be so involved, but that alone is not specific, as it occurs also in congenital hemolytic jaundice. The anomaly characteristic of sickle cell anemia is the pronounced malformation of the sinuses immediately about the Malpighian bodies, leading to the formation of pools of blood partially or completely surrounding the Malpighian bodies. This is referred, for reasons discussed, to imperfections in the ampullae of Thoma. There is frequently, besides, an abnormal development of capillaries throughout the Malpighian body. The vascular abnormalities in and immediately about the Malpighian bodies may or may not be associated with the free escape of blood into the general splenic pulp. The reticulum of the spleen is not primarily abnormal. Other details of the pathology of the condition in the spleen and other organs were discussed and will be published in a more complete paper. The anemia in the active cases is of the characteristic "hemolytic" type, and we were able to demonstrate, therefore, an abundance of hemosiderin in the tissues, in contrast to the report of Sydenstricker.

The existence of the sickle cell trait can be easily and surely recognized by the specific histological appearance of the spleen.

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